DOCUMENT RESUME

ED 168 857 SE 026 938

TITLE	Advisory Report on the Health Effects of Radium 226 in Drinking Water.
INSTITUTION	Illinois Inst. for Environmental Quality, Chicago.
REPORT NO	IIEQ-77-12
BUREAU NO	90.002
PUB DATE	Jun 78
NOTE	81p.
EDRS PRICE	MF01/PC04 Plus Postage.
DESCRIPTORS	*Environmental Education; Health; Natural Resources; *Public Health; *Radiation Effects; *Radioisotopes; Safety; Science Education; Water Pollution Control; *Water Resources

ABSTRACT

Examined are the health effects of law concentrations of the radioactive isotope Radium-226 in drinking water. Contents include discussions of the physical properties of radium, biological and metabolic effects, health effects of exposure to Radium-226, and populations at risk. Appendices provide more technical information including equations, charts, graphs, and a glossary of terms. Sixty-three references are given. (MA)

****
* Reproductions supplied by EDRS are the best that can be made *
* from the original document. *
****

ED168857

SE

ILLINOIS INSTITUTE FOR ENVIRONMENTAL QUALITY

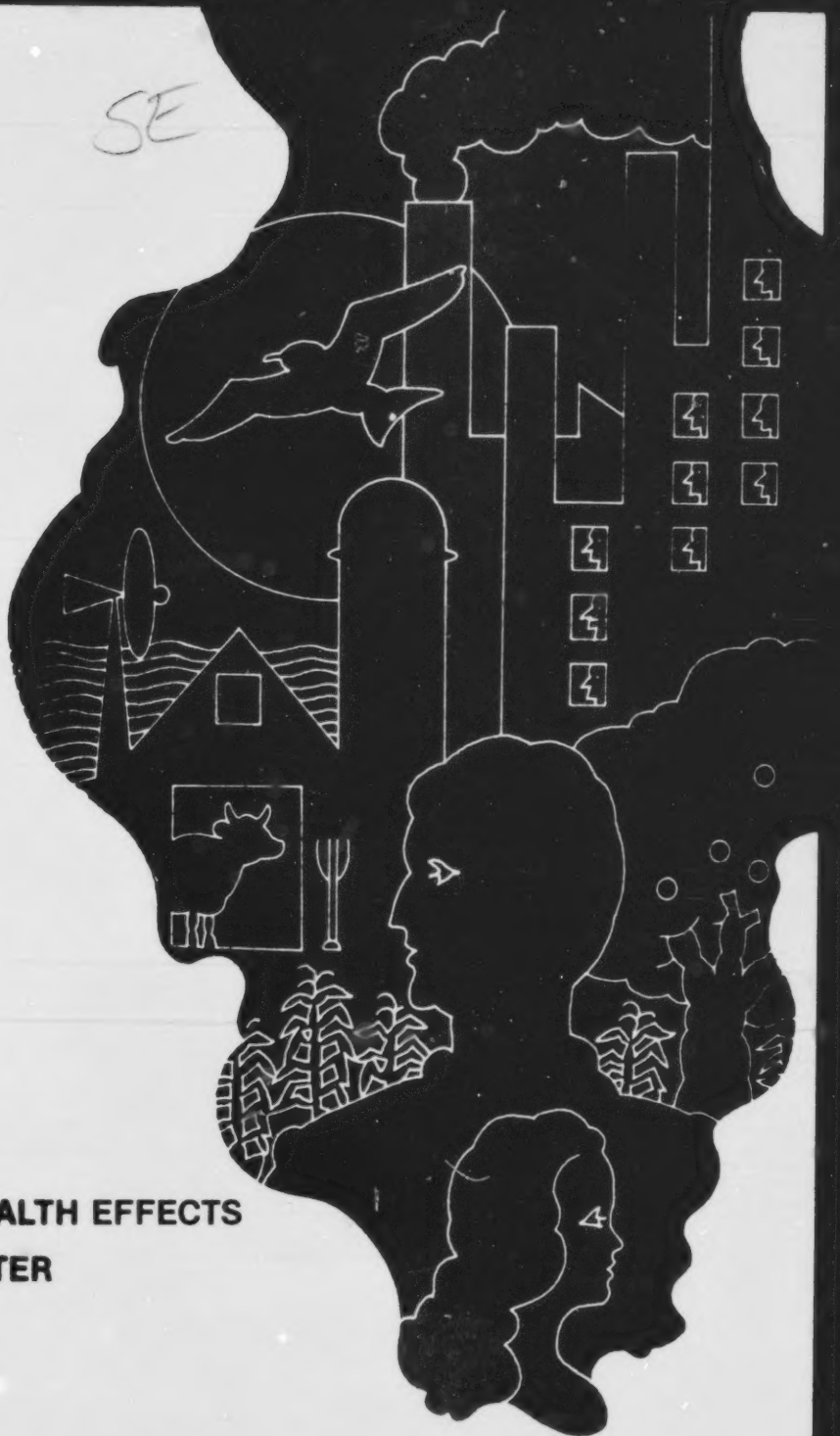
U.S. DEPARTMENT OF HEALTH, EDUCATION & WELFARE
NATIONAL INSTITUTE OF EDUCATION

THIS DOCUMENT HAS BEEN REPRODUCED EXACTLY AS RECEIVED FROM THE PERSON OR ORGANIZATION ORIGINATING IT. POINTS OF VIEW OR OPINIONS STATED DO NOT NECESSARILY REPRESENT OFFICIAL NATIONAL INSTITUTE OF EDUCATION POSITION OR POLICY

"PERMISSION TO REPRODUCE THIS MATERIAL HAS BEEN GRANTED BY

Eunice Choi

TO THE EDUCATIONAL RESOURCES INFORMATION CENTER (ERIC) AND USERS OF THE ERIC SYSTEM."



ADVISORY REPORT ON THE HEALTH EFFECTS OF RADIUM^{226} IN DRINKING WATER

SE 026 938

IEQ Document No. 77/12

ADVISORY REPORT ON THE HEALTH EFFECTS OF RADIUM ^{226} IN DRINKING WATER

by the

Environmental Health Resource Center

Project No. 90.002
(EHRC Doc. No. 20)

IIEQ Document No. 77/12

State of Illinois
Institute for Environmental Quality
Frank Beal, Director

June, 1978

NOTE

This report has been reporduced as received from the contractor. No editorial or other changes have been made. Conclusions expressed are the contractor's.

Printed by Authority of the State of Illinois

Date Printed: June, 1978
Quantity Printed: 150

This document has been cataloged as follows:

Illinois Institute for Environmental Quality
Environmental Health Resources Center
Advisory report on the health effects of Radium^{226} in drinking water. -- Chicago : Illinois Institute for Envionmental Quality, 1978

75 p. ; 28 cm. -- (IIEQ Doc. No. 77/12; EHRC Doc. No. 20)

1. Drinking water - health 2. Radium Isotopes - drinking water 3. Radium Isotopes - toxicity 4. Drinking water - Illinois I. Title II. Environmental Health Resource Center

IIEQ Environmental Information Center

Illinois Institute for Environmental Quality
309 West Washington Street
Chicago, IL 60606
(312) 793-3870

TABLE OF CONTENTS

		page
I.	FOREWARD	1
II.	Radium - Non-Technical Summary	2
III.	Rationale	4
IV.	Recommendations for Further Research	9
V.	Sources and Levels of Gross α and ^{226}Ra Activity in Illinois Water Supplies	10
VI.	Radium - Physical Properties, Biological Effects and Metabolism	13
	A. Physical Properties	13
	B. Biological Effects	16
	C. Metabolism: Absorption, Distribution, Retention and Excretion	19
VII.	Health Effects of Exposure to ^{226}Ra	24
	A. Animal Studies	24
	B. Acute Exposure - Human	25
	C. Chronic Exposure - Human	27
	D. Non-carcinogenic Effects of ^{226}Ra Exposure	30
	E. Calculation of ^{226}Ra Body Content	31
VIII.	Populations at Risk	32
	A. Age as a Sensitivity Factor	32
	B. Enzyme and Metabolism Deficiencies	33
IX.	Appendices	36
	A. Physical Properties	36
	B. Biological Effects	46
	C. Metabolism	54
	D. Glossary	67
X.	References	70

ENVIRONMENTAL HEALTH RESOURCE CENTER

P.O. Box 6998, Chicago, Illinois: Phone: (312) 996-2591

CENTER STAFF
at the
University of Illinois School of Public Health
Occupational and Environmental Medicine (OEM)

Bertram W. Carnow, M.D.
Center Director
Professor and Director, OEM

Rod Musselman, M.P.H.
Center Assistant Director
Instructor, OEM

Badi M. Boulos, M.D., Ph.D.
Associate Professor, OEM

Daniel Brachman, M.P.H.
Instructor, OEM

Christine R. Riddiough, M.S.
Research Associate, OEM

Zanet Flournoy-Gill, M.P.H.
Research Associate, OEM

Sally J. Jansen, M.P.H.
Research Associate, OEM

Gail Barazani, B.A.
Research Associate, OEM

Edward Bouchard, B.A.
Research Assistant, OEM

Sara Green, B.A.
Research Assistant, OEM

Leslie Schuster, B.A.
Research Assistant, OEM

ADVISORY BOARD

R. Stephen Berry, Ph.D.
Professor of Chemistry
University of Chicago

Samuel S. Epstein, M.D.
Professor, OEM
U of I School of Public Health

Edward R. Hermann, Ph.D.
Professor, OEM
U of I School of Public Health

Paul Meier, Ph.D.
Professor of Statistics
University of Chicago

Robert L. Metcalf, Ph.D.
Professor of Entomology
University of Illinois-Urbana

William Murphy
Environmental Scientist
Illinois Institute for
Environmental Quality

J. E. Quon, Ph.D.
Professor, Civil Engineering
Northwestern University

The Environmental Health Resource Center is an arm of the Institute for Environmental Quality, managed under contract with the Institute, by the University of Illinois School of Public Health at the Medical Center, Chicago, Illinois.

I. FOREWORD

This document deals with the health effects of radium-226 (^{226}Ra) in drinking water. It was researched and written by Rod Musselman, M.P.H. and Christine Riddiough, M.S. of the Institute's Environmental Health Resource Center. The material presented was prepared through a synthesis of the literature and under the direction of critical reviews of that synthesis by the Advisory Board. Recommendations for further research are made both as a guide for research agencies and as a report of the state of the art with respect to ^{226}Ra.

The Institute's Environmental Health Resource Center wishes to thank Mrs. Patricia Sawyer and Mrs. Alberta Braden for typing early drafts of this document and Mrs. Patricia Schaffner for typing the final copy.

II. RADIUM - NONTECHICAL SUMMARY

Radium-226 (^{226}Ra), discovered in 1898 by Marie and Pierre Curie, is a white metal that blackens on exposure to air. It is a radioactive substance that emits α (alpha) particles. As an alkaline earth element (such as calcium and barium), it replaces calcium in bones, concentrating in that organ, so most of its health effects occur in bone. Because it occurs naturally at low levels in some drinking water supplies, it is ingested by many people and then is deposited in the bone. It can affect the cells in several ways. As the alpha particles are emitted they can react with the water of the cells to create hydrogen peroxide, which can then disrupt the normal functioning of the cell. Such particles can also attack the basic genetic material (DNA and RNA) directly.

Both human and animal studies have been done to examine the health effects of ^{226}Pa. Although radium has several different isotopes, this document is primarily concerned with ^{226}Ra. Only a few of the available animal studies on the effects of ^{226}Ra are useful in the consideration of the effect of low doses of ^{226}Ra. The limited usefulness of such studies is due to the small number of animals tested, and the single, high, or unknown doses used. Those studies which have yielded useful results indicate that ^{226}Ra causes bone cancer, at least at high doses. Human studies have focused on the effects of high doses of ^{226}Ra, but it can be misleading to assume that health effects from low doses (such as found in drinking water) are proportional to the health effects from high doses, such as those received by radium dial painters. Studies of radium dial painters (who used small paint brushes to paint dials with radium, putting the brushes between their lips to form a tip), and others indicate radium is a cause of bone cancer in humans. Only one study has been done on the effects of low doses of ^{226}Ra.

While the results of the study were not statistically significant, (equivocal), they did point to the possibility that those using such drinking water did have higher rates of bone cancer than others. The young (under eight years) seem to be particularly susceptible to the effects of ^{226}Ra.

The EHRC advises that further research be done in order to better understand the health effects of ^{226}Ra at low concentrations. Research studies are recommended for the following areas:

1. Epidemiological studies concerned with cancer induction from ^{226}Ra in drinking water.
2. Studies concerned with the determination of ^{226}Ra effects at the cellular and sub-cellular level. Such studies should determine how chromosome aberrations are affected by the presence of ^{226}Ra in drinking water.

Research studies in these two areas will be of great assistance for defining groups of individuals who may be at high risk to ^{226}Ra.

III. RATIONALE

There are several different theoretical approaches to the question of standard setting for ^{226}Ra in drinking water. The main concern of all approaches considered here is to define the relationship between cancer and ^{226}Ra body burden (i.e., the "dose-response" relationship). Since sufficient human data upon which to make a definitive judgment are lacking, no single approach is universally accepted.

The U.S. Environmental Protection Agency (EPA) based its proposal for maximum contaminant levels for ^{226}Ra in drinking water on earlier guidelines from the International Commission on Radiological Protection (ICRP),[1,2] the National Academy of Sciences Report of the Advisory Committee on the Biological Effects of Ionizing Radiation (NAS-BEIR Report)[3], and the Federal Radiation Council.[4] They relate ^{226}Ra ingestion to body burden and dose and thence to cancer risk via a linear extrapolation model (LEM). All of the aforementioned reports[1-4] are concerned with ^{226}Ra exposure at high dose levels (>100 rads cumulative). Information and models developed therein are based primarily on studies of radium dial painters, patients exposed to radium during medical treatment and atomic bomb survivors. Based on the LEM, EPA has extrapolated from the health effects encountered at high levels of ^{226}Ra exposure to their projected health effects from low levels of ^{226}Ra exposure in drinking water (a concentration that results in approximate 1 rad dose). This extrapolation may be misleading since it implies that the nature of the dose response curve at low doses can be determined by data derived from the high dose range.* Yet the nature of the curve can only be verified by observations at

*An example of the potential errors inherent in such extrapolation is given by the safety testing of the Salk poliomyelitis vaccine as reported by Cornfield, J., Halperin, M., and Moore, F., "Some Statistical Aspects of Safety Testing of Salk Poliomyelitis Vaccine" Pub. Health Rep., 71, 1045-1056, (1956).

low doses, which would require and epidemiological study of sufficient size to show significant differences between groups with low exposure levels.

It should be emphasized that linear extrapolation of health effects caused by high LET (linear energy transfer) radiation may underestimate the potential hazard because the carcinogenic risk per rad may increase as the dose and dose rates are decreased.[38] Furthermore, the LEM predicted 5 to 28 malignant bone cancers for the Peterson study (as described below), but 30 such tumors were noted.

On the basis of such extrapolation, U.S. EPA has made risk estimates for cancer induction by ^{226}Ra. EPA asserts that their estimates are uncertain by a factor of four or more. On the basis of such estimates, U.S. EPA has set its control limit for ^{226}Ra at 5 pCi/liter (See Table I, "Epa" for US EPA risk estimates.)

Another approach is that of Gofman and Tamplin, which is also based on cancer incidence for high doses of ^{226}Ra.[5] They base their risk estimates on data from studies of radium dial painters and exposure to several types of radiation. Gofman and Tamplin approach the question of dose-response differently in that they view cancer induction as a function of dose, time after exposure and age at exposure. They suggest: (1) there is a latency period during which cancer does not develop, this latency period being shorter for in utero exposure than otherwise (5 years vs. 15 years for all irradiation beyond birth); (2) there is a plateau region with variable duration for each dosage. The plateau region representing the age-specific mortality rates for radiation induced cancers. (This plateau may be finite in duration which indicates a return to the spontaneous mortality rate, or infinite in duration, which indicates no return.); (3) the number of radiation induced cancers decreases with increasing age at time of exposure; (4) there is a linear dose-response relationship with the latent period the

same for all doses. Furthermore, safety dictates the adoption of a cautious rather than an optimistic relationsip.

Gofman and Tamplin then examined human carcinogenic responses to present levels of total estimated radiation exposure under different theoretical post-natal latency and plateau periods.

The data from the three cases can be used to calculate a dose-response relationship analogous to U.S. EPA's prediction. The dose-response estimate of Gofman and Tamplin (Rgt) is given in Table I as the range from the low risk estimate to the high risk estimate. Much the same criticism of these risk estimates can be made as above for the U.S. EPA. Again, extrapolation from high to low levels is involved and all the problems inherent therein. Finally, the research of Jones and Grendon (discussed more fully below) suggests that the latency period is also, in part, dependent on dose, in direct contrast to assumption No. 4 of Gofman and Tamplin.

Thirdly, Evans, based on his studies of radium dial painters and others, concluded that there is a "practical" threshold where the latency period is longer than normal life expectancy.[6] The smallest body burden to produce a tumor reasonably attributable to ^{226}Ra is 1.23 μCi. From the U.S. EPA calculations, the ingestion of 5 pCi/liter results in a body burden of 500 pCi or 5×10^{-4} μCi, well below the Evans limit.[7] Jones and Grendon derived a similar dose-effect relationship for a variety of chemical carcinogens (hydrocarbons) as well as ionizing radiation.[8] Based on animal and human data (including Evans[6]), they suggest that latency period is inversely proportional to dose. For a ^{226}Ra body burden of 0.1 μCi they calculate a latency period of 83 years; this tends to support the "practical threshold" concept of Evans.[6] However, both Evans[6] and Jones and Grendon[8] are subject to criticism of their analyses of data. First of all, extrapolation from high doses to low doses is easily subject to error; this is especially true when limited data are used (as is the case with Jones and Grendon[8]). Further, calculation of dose is dependent on the retention function used and this will affect the dose-response

relationship. Calculation of tumor appearance times giving the 95 percent confidence limits indicates that the lower limit may be as low as 11 years for a cumulative dose of 700 rads; this obviously calls into question the practical threshold concept. Jones and Grendon's calculation of latency period is also questionable, as is Evans' use of a scale based on bone x-rays to quantify health effects. Because of these criticisms, one cannot give much weight to the concept of a practical threshold.

Alternately, epidemiological studies can be used in support of a standard. So far there is one such study, that of Peterson et al.[9] In this approach, the number of cancers are considered to be a function of four variables to which the population is exposed: 1) amount of ^{226}Ra, 2) amount of other α radiation, 3) amount of non-α radiation, and 4) amount of non-radiation carcinogens. Assuming that the effects of the various carcinogens are additive, the numbers of cancers caused by ^{226}Ra can be distinguished from the other three variables. From epidemiological studies, only the total number of cancers induced by all carcinogens can be recorded. If one assumes that proper controls have been placed on all other factors, then the only variable that can affect cancer induction will be the amount of ^{226}Ra in drinking water. Thus risk associated with various levels of ^{226}Ra can be calculated. This is indicated in Table I as Rp (dose-response relationship of Peterson). This estimation has the advantage of being based on doses of the order of magnitude that would occur for levels of ^{226}Ra known to be in water; thus, they are more closely related to the standard itself. However, the available data are limited and have not been confirmed by other epidemiological studies.

TABLE I

RISK ESTIMATES FOR CANCER

^{226}Ra Concentration in drinking water (pCi)	Cancers Due to ^{226}Ra per 10^6 persons per year			
	Repa *(a)*	Rgt *(b)*	Re *(c)*	Rp *(d)*
1	.14- .6	.5 - 5	0	1.26
2	.28-1.2	.9 -10	0	1.96
3	.42-1.8	1.4 -15	0	2.66
4	.56-2.4	1.9 -20	0	3.36
5	.70-3.0	2.41-25	0	4.06

(a) U.S. EPA; (b) Gofman and Tamplin; (c) Evans; (d) Peterson

Four different approaches have been described which attempt to predict the human health risks associated with different possible drinking water standards for ^{226}Ra. As a result of insufficient data, strong confidence in any particular approach is lacking. However, it is important to note that three (Repa, Rgt, Rp) of the four approaches demonstrate partial agreement with respect to the general level of carcinogenic risk. Also Repa and Rp are in extraordinarily close agreement at all possible standards considered. Thus, considerable agreement does exist between both the linear extrapolation and epidemiologic models. Agreement from such diverse approaches adds considerable confidence that their postulated cancer frequencies are reasonable predictions. However, only the Rgt model incorporates a specific consideration of a high risk segment in the population (the very young), although the Peterson, *et al* study indicated that age may be a factor in susceptibility. This consideration for high risk populations accounts, in part, for the higher Rgt model estimates of cancer incidence. The very young, it should be emphasized, are considered at high risk not only because of the large number or rapidly dividing and differentiating cells, but also because they are thought to absorb radium more efficiently through the gastrointestinal

tract than adults.[10] They also have a longer potential latent period.

In setting a standard for ^{226}Ra in drinking water, attention must be given to the basic agreement between the linear dose relationship and epidemiologic model prediction, the increased carcinogenic risk at low levels of high LET exposure and the need to insure adequate protection to high risk segments of the population. The EHRC takes the position that there can be no safe level for exposure to any carcinogenic agent, including ^{226}Ra. In light of this, the risk estimates for cancer given in Table I indicate cancer as the primary limiting health factor for ^{226}Ra and must be carefully considered in the setting of any standard.

IV. RECOMMENDATIONS FOR FURTHER RESEARCH

In order to increase understanding of the health effects of ^{226}Ra, further research is recommended in the following areas:

1. Further epidemiological studies concerned with cancer induction by ^{226}Ra in drinking water should be conducted. Illinois is unusual in having a substantial (>800,000 people) portion of its population using drinking water from sources with high levels of ^{226}Ra. This makes it an important area of study. Such epidemiological studies may also lead to a better understanding of the carcinogenic properties of low levels of other emitters, such as plutonium.
2. Studies should be done to determine ^{226}Ra effects at a cellular and subcellular level. Studies should determine how chromosome aberrations are affected by the presence of ^{226}Ra in drinking water.
3. Better definition of groups of individuals at high risk to ^{226}Ra should be made.

V. SOURCES AND LEVELS OF GROSS α AND ^{226}RA ACTIVITY IN ILLINOIS WATER SUPPLIES

Since the 1950's, a number of surveys have been undertaken to determine levels of radioactivity in drinking water supplies of several states.[23-29] Some of these have investigated gross α activity, while others have looked specifically for ^{226}Ra activity. There is, unfortunately, no easy way to relate gross α to ^{226}Ra activity; estimates of ^{226}Ra activity based on gross α may be an order of magnitude off, since gross α activity will include activity from a variety of nuclides, among them ^{226}Ra. Gross α is measured by proportional counting of the non-volatile residue remaining after evaporation of the water carrier. Radium-226 activity cannot be estimated from this for several reasons. ^{226}Ra may occur either on the surface of the carrier or below the surface, thus affecting the count rate; both ^{226}Ra and ^{228}Ra will give rise to radon (Rn) daughters which will also complicate the results. However, further analysis will allow determination of ^{226}Ra activity.[11,12] After evaporation of the carrier, the Rn daughters will have been evaporated, thus leaving ^{226}Ra and ^{228}Ra. Since the half-lives of the two isotopes are different, a series of three counts several hours apart will allow the separation of ^{226}Ra and ^{228}Ra activity.[11,12]

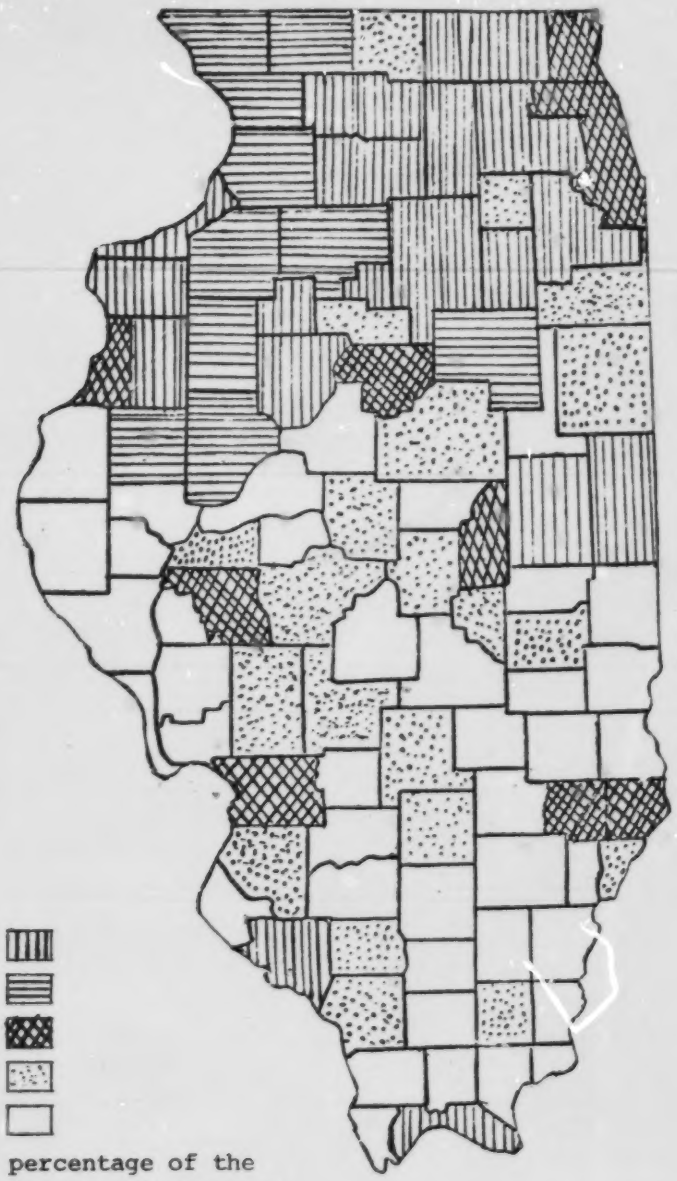
The presence of varying amounts of ^{226}Ra and gross α activity in many drinking water wells in Illinois is firmly established. In 1958, Lucas and Ilcewicz analyzed 200 water samples for ^{226}Ra from 159 municipal water supplies.[13] These samples were taken from wells located in deep sandstone (Cambrian and Ordovician rocks), shallow sandstone (Pennsylvanian rocks) and limestone (Mississippian, Devonian and Silurian rocks). Lucas and Ilcewicz found variations in the ^{226}Ra concentrations according to the location of the well. For example, unconsolidated (glacial drift) well water and surface waters had ^{226}Ra mean values of 0.10 and 0.28 pCi/liter, respectively. Wells located in limestone

formations had a mean concentration of 0.37 pCi/liter. For wells located in deep sandstone, the ^{226}Ra concentration in the water ranged from 1 pCi/liter to over 25 pCi/liter. The mean concentration was 6.0 pCi/liter of ^{226}Ra. Water containing high concentrations of ^{226}Ra is then associated primarily with wells located in the St. Peter sandstone formation.[14] The St. Peter sandstone was formed during the Ordovician geologic period and is found in deep bedrock valleys in northern Illinois and along the Illinois River.[13] In 1962, the Midwest Environmental Health Study[3] was initiated by the Division of Radiological Health of the U.S. Public Health Service to undertake an epidemiologic investigation of human populations exposed to elevated levels of ^{226}Ra in drinking water (this includes the Peterson study referred to below).[9,15]

In 1972, the Illinois Environmental Protection Agency (IEPA) conducted a water analysis program in order to determine the levels of toxic substances (e.g. barium, nitrates and radioactivity).* The agency listed 286 communities and state parks which were serviced by water supplies whose gross α concentrations were in excess of 3 pCi/liter.[16]

The Environmental Health Resource Center (EHRC) found that 205 of these communities were listed in the 1970 Census. The remaining 81 sites were parks or communities too small to be recorded in the Census.# Based on information derived from the IEPA and the 1970 Census, the EHRC identified and quantified possible populations at risk to ^{226}Ra exposure. Table II shows that of the total of 205 water supplies, 80 water supplies serving 842,246 people had a mean (population weighted) concentration for alpha activity of 13.5 pCi/liter.[16,*,#] The range of the concentration of 122 samples that were taken from these 80 water supplies was from 3.4 pCi/liter to 66.6 pCi/liter. Each of the 80 water supplies analyzed had at least one value that was equal to or greater than 10 pCi/liter. Of the 842,246 people exposed to these

Figure 1: Map of the State of Illinois Indicating Those Counties Served by Drinking Water Supplies Containing Three Picocuries per Liter or More Gross Alpha Activity.



P is the percentage of the population in each county served by drinking water supplies containing three picocuries or more gross alpha activity.

levels of activity, at least 13,396 persons were under the age of one year, 72,560 were under the age of five years, and at least 298,655 persons were under the age of 18 years.[16,*,#]

Table III presents data for 125 municipalities with reported gross α levels ranging from greater than 3 pCi/liter to less than 10 pCi/liter. The mean (population weighted) concentration of activity for the 133 samples analyzed was 5.1 pCi/liter. These water supplies serviced 687,173 persons in 1970, of whom at least 7,717 were less than one year old, 55,559 were less than five years of age, and at least 236,805 were less than 18 years old.[36,*,#] Figure 1 indicates the location of these communities.

VI. RADIUM - PHYSICAL PROPERTIES, BIOLOGICAL EFFECTS AND METABOLISM

A. Physical Properties

Radium, discovered in 1898 by Marie and Pierre Curie, is a white metal which blackens on exposure to air; its melting point is 700°C and its boiling point is 1140°C. Radium has an atomic number of 88 and has 13 known isotopes, all of which are radioactive. The most important isotope, and the one of concern herein, is ^{226}Ra, which forms part of the uranium series (beginning with ^{238}U). Its half-life is 1622 years and its transformation (daughter) product is ^{222}Rn (radon, a gas). The rest of the series is discussed in Appendix A.

**Letter from Mr. Jack M. Marco, Acting Director, Illinois Environmental Protection Agency, 2200 Churchill Road, Springfield, Illinois to Mr. Samuel Booras, Director, Institute for Environmental Quality, 309 West Washington, Chicago, Illinois, May 1, 1973.*

#Personal communication of Rod Musselman and Christine Riddiough to Dorothy Bennett, Division of Public Water Supplies, Illinois Environmental Protection Agency, 2200 Churchill Road, Springfield, Illinois 62706, December, 1975.

TABLE II

SUMMARY OF ILLINOIS COMMUNITIES WITH ONE OR MORE REPORTED GROSS α CONCENTRATIONS EQUAL TO OR EXCEEDING TEN PICOCURIES PER LITER OF DRINKING WATER

Population Category *(a)* (1970)	Number of *(b)* Cities	Number of *(b)* Samples	Range of Gross α Concentrations *(b)* (pCi/liter)	Mean Concentration Gross α *(b)* (pCi/liter)	Total Population Exposed *(b)*	Numbers and Ages of People Exposed *(a)* Under 1 year	Under 5 years	Under 18 years
50,000 or more	6	17	5-26.6	13.6	382,208	6,555	32,237	129,157
10,000-50,000	19	32	3.4-28	11.7	368,923	6,841	36,279	143,427
2,500-10,000	13	21	4-66.6	19.2	52,034	NA *(c)*	4,044	17,266
1,000-2,500	16	21	6-44.7	22.0	25,528	NA *(c)*	NA *(c)*	8,805
Less Than 1,000	26	31	4.3-44	20.7	13,553	NA *(c)*	NA *(c)*	NA *(c)*
Totals	80	122	3.4-66.6	13.5*	842,246	13,396	72,560	298,655

(a) Bureau of the Census, General Population Characteristics: Illinois, U.S. Department of Commerce, PC(1) - B15 Ill., October, 1971

(b) Data from Illinois Environmental Protection Agency, Division of Public Water Supplies, 220 Churchill Road, Springfield, Illinois, 62706, November, 1973.

(c) Not Available.

**Population Weighted Mean*

TABLE III

SUMMARY OF ILLINOIS CITIES AND TOWNS WITH REPORTED GROSS α CONCENTRATIONS EXCEEDING THREE PICOCURIES BUT LESS THAN TEN PICOCURIES PER LITER OF DRINKING WATER

Population Category (a) (1970)	Number of (b) Cities	Number of (b) Samples	Range of Gross α Concentrations (b) (pCi/liter)	Mean Concentration Gross α (b) (pCi/liter)	Total Population Exposed (b)	Numbers and Ages of People Exposed (a) Under 1 year	Under 5 years	Under 18 years
50,000 or more	2	2	3.5-3.9	3.7	187,268	3,064	15,554	64,823
10,000-50,000	15	15	3.1-9.0	5.5	267,382	4,653	24,010	98,869
2,500 - 10,000	32	33	3.1-9.7	5.8	163,549	NA (c)	15,995	58,448
1,000-2,500	26	29	3.1-9.5	5.6	42,301	NA (c)	NA (c)	14,665
Less Than 1,000	50	54	3.1-9.6	5.3	26,673	NA (c)	NA (c)	NA (c)
Totals	125	133	3.1-9.7	5.1*	687,173	7,717	55,559	236,805

(a) Bureau of the Census, General Population Characteristics: Illinois, U.S. Department of Commerce, PC(1) - B15 Ill., October, 1971.

(b) Data from Illinois Environmental Protection Agency, Division of Public Water Supplies, 220 Churchill Road, Springfield, Illinois, 62706, November, 1973.

(c) Not Available.

**Population Weighted Mean*

An understanding of the effect on human health can be enhanced by looking at the nature of radiation and its interaction with molecules. In this document "radiation" means energy from electromagnetic interactions; this follows the law:

$$E = h\nu \qquad \text{(Eq. 1)}$$

with E = energy, h = Planck's constant (6.6256×10^{-27} erg sec.) and ν = frequency.

The concern of this paper is primarily α particles, since ^{226}Ra is primarily an α emitter and α particles are considered to be potentially at least ten times as destructive as β particles.[2,17] They are helium nuclei ($^{4}_{2}He$). Their energy and frequency (from experiments and the above equation) is on the order of five million electron volts and 1.2×10^{-21} per sec.[12] Alpha particles are easily stopped by a piece of paper and in the body by intimate contact with cells. For a more complete description of the physics of radiation see Appendix A.

B. Biological Effects

Radiation can affect cellular processes in several ways. Its ionizing effect on water molecules, producing hydrogen peroxide (H_2O_2) and free radicals is a particularly important one. Hydrogen peroxide is a strong oxidizing agent and will disrupt the cell through activities such as the detachment of amine groups from amino acids, removal of carboxyl groups from organic acids, oxidizing sulfhydryl (SH) compounds, and decomposing simple sugars, such as glucose. The pyrimidine bases (thymine, uracil, cytosine) of DNA and RNA may also be attacked. Each of these bases is a hexagonal ring compound with two nitrogens and a double bond between the fifth and sixth carbon atoms. This double bond is attacked producing radical intermediates which have an unpaired electron at the five positions. These radicals will pick up the H^+ and OH^- radicals to form relatively stable end products. This is likely to affect the coding of DNA and RNA, leading to

mutations of potentially far-reaching significance (including the possible production of altered protein). The α particle, in particular, can also attack the DNA directly (Figures 2 and 3; see also Appendix B). The biological effect of radiation will depend on the dose, the rate of dose administration (or dose fractionation) the energy and type of radiation and the cell sensitivity.

1. Dose: For biological entities, like cells, molecules and viruses, the number inactivated in a group depends on the dose received. In general, the higher the dose, the greater the number of entities inactivated. For entities which require only one hit to inactivate them, the inactivation rate will follow a simple exponential law; for entities that require more than one hit, the situation is more complex because repair of the entity can take place between hits.[18,19]

2. Dose Rate: For one hit entities (as above) the rate at which the dose is delivered will not affect the biological response. However, if more than one hit is required to inactivate a target, dose rate may be a factor.[18,19] This is particularly true where repair takes place, since, if the dose rate is low, the target might be able to repair itself between hits. Studies on gene mutation production in mice suggest that higher dose rates are more effective in producing permanent mutations.[18]

3. Dose Distribution: For objects (such as bone, brain or whole organisms) made up of more than one entity, dose distribution will also be a factor. For macroscopic effects like carcinogenesis to appear, proximal cells must be altered. Consequently, spatial distribution of the dose is important.[8]

4. Cell Cycle: Cells undergoing mitosis (nuclear division) are generally more sensitive to the effects of radiation than those in the non-mitotic phase. However, within the mitotic phase there appears to be variation between species in regard to radio-sensitivity of different stages of nuclear division. For example, tests on cell survival rates at different times of the

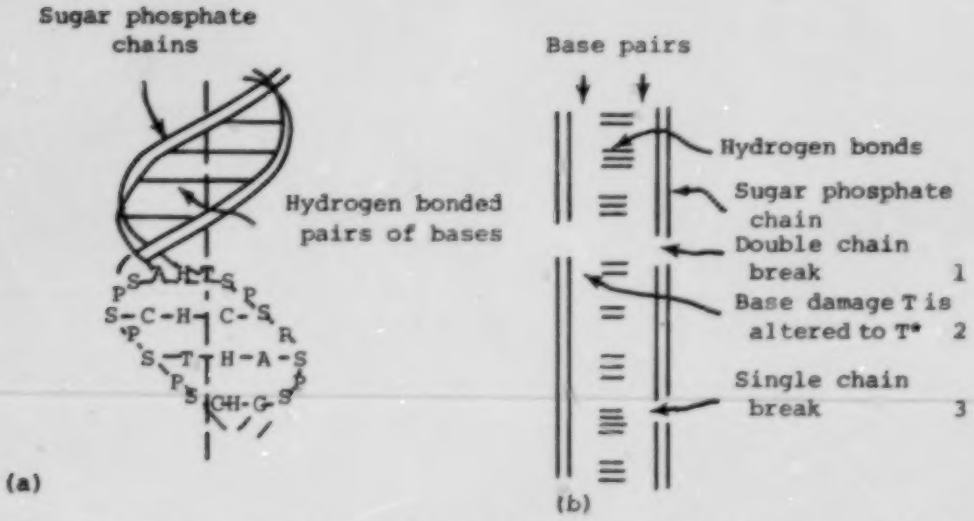


Figure 2: (a) Schematic representation of DNA showing the double helix, the sugar phosphate chains, and base pairs.
(b) Three possible types of damage in DNA.[19]

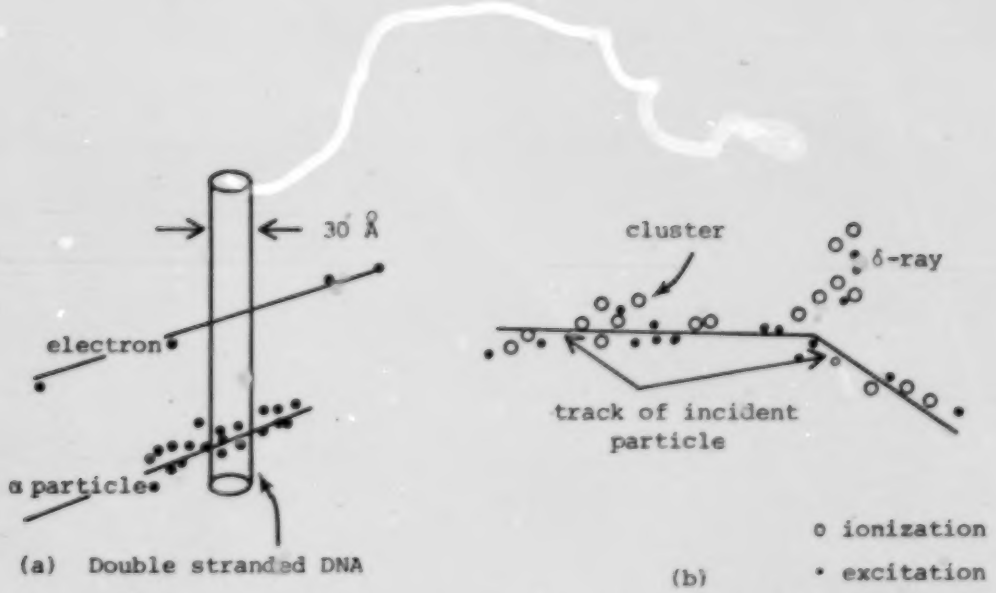


Figure 3: (a) Schematic representation of DNA and the tracks of an electron and an α particle through it.
(b) Schematic drawing of a charged particle track.[19]

mitotic cycle, indicate that for some cells (mouse L) the late part of DNA synthesis is the most sensitive while for others (Chinese Hamsters), it is the least sensitive.[18] (See Appendix B)

C. Metabolism: Absorption, Distribution, Retention and Excretion.

Before discussing the metabolism of radium within the body, the structure of bone, including its formation and growth, and the distribution of minerals in the bone, will be discussed. This is necessary since radium, like the other alkaline earth elements, is a "bone-seeker" and so most of its effects are concentrated on the bone tissue.[19]

The bony skeleton serves as the framework for the body, provides points of attachment for the muscles, and stores the bone marrow and most body calcium.[19] The bones are not a static system; there is a turnover of 0.5 g/day of calcium, even in adults. This calcium is used in the formation of new bone and the resorption of old bone. Microscopically, bones have two types of structure; the hard cortical bone that generally forms the outer wall (Figure 4) and the trabecular bone which is spongy and light and which provides a network in which the marrow is generally located. The end of the bone is called the epiphysis, and it is separated from the rest of the bone by a cartilage plate. The other side of the plate is the metaphysis, and it is an area of much bone growth activity. Along the shaft of the bone there is a thin membraneous covering called the periosteum; inside the periosteum is a cell lining called the endosteum. These two regions are associated with the growth and repair of bone. Bone growth does not occur simply by cell division, since the soft tissues of the bone are enclosed in a calcified matrix - this gives the bone its distinctive structure. In the process of remodeling, new bone is added to the skeleton and old bone removed (apposition and resorption, respectively). This process continues throughout life. Growth occurs longitudinally and circumferentially. In the first case, the site of growth is the cartilage plate, and in the second, the periosteal and sometimes, the

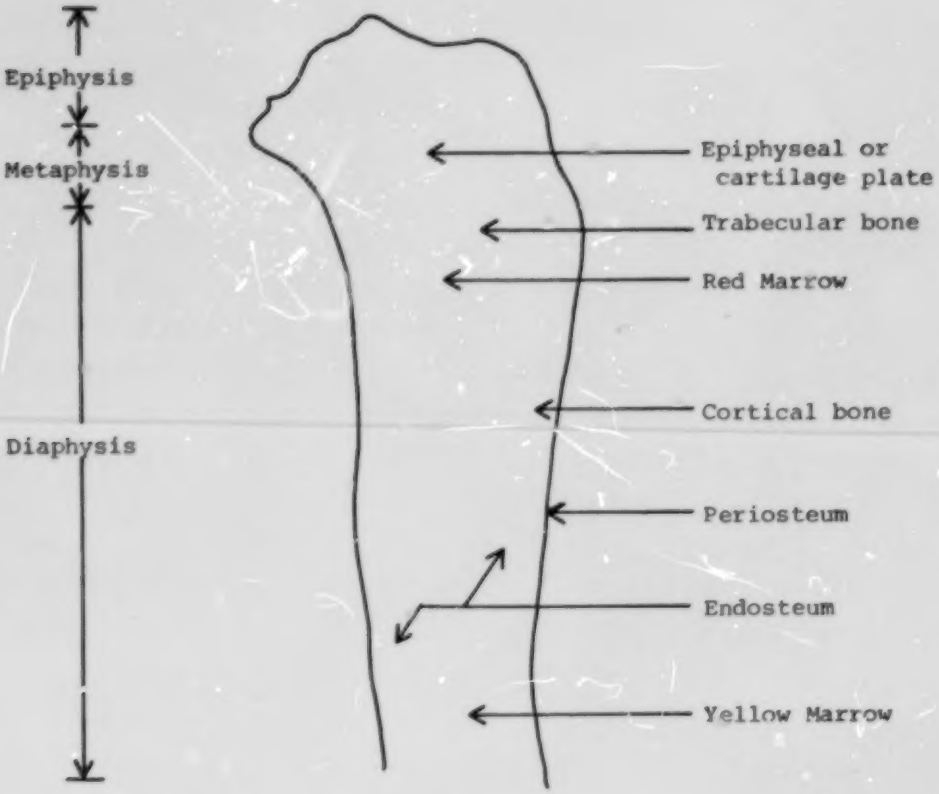


Figure 4: Section of upper part of the human tibia (schematic).[19]

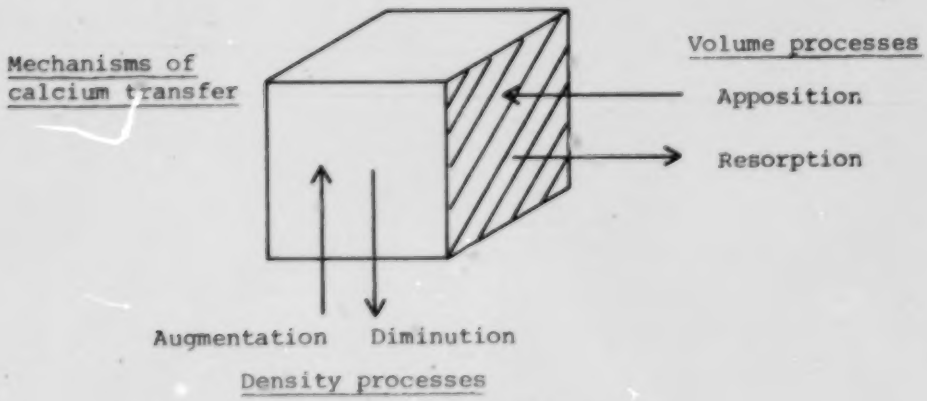


Figure 5: Diagram of a bone volume element and mechanisms of calcium transfer.[19]

endosteal surfaces.[20]

Bone is made up of three kinds of cells; osteoblasts, osteocytes and osteoclasts. The first are associated with bone formation. Active osteoblasts are found in the periosteal layers, in the cartilage, in active marrow and in the spine. They lay down the material that calcifies. The osteocytes are associated with the maintenance of bone as living tissue. The osteoclast is a large cell associated with the resorption process. Typically, the osteoblasts will invade a region and lay down material that will calcify. An artery will grow into the cavity (Haversian canal) and the osteocytes will build up around it. They will be connected by the canaliculi (fine channels in the calcified matrix of the bone). The bone mineral is thought to be composed of the salt, hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), with other minerals possibly present. Other ions, Pb^{2+}, Ra^{2+}, Sr^{2+} can be substituted for the calcium while still maintaining the crystal lattice. This salt is not very soluble in tissue fluids so that the skeleton maintains its rigidity. Since the crystals are small, a large fraction of the material is exposed to surface chemical effects. Because of this exposure, ion exchange can take place rapidly, while within the crystal, exchanges occur more slowly. Because ^{226}Ra can be substituted for calcium in the bone mineral, it is found throughout the bone. The radiation effects, however, are found not in the crystal, but in the living cell of the bone, which is more sensitive than the intercellular material.[20]

Radium is introduced to the bone in two major ways; apposition and augmentation. Radium can be removed from the bone in two analogous ways, resorption and diminution. Apposition occurs at the surface of the bone and is a part of the process of bone growth, for it provides a change in the volume of bone. Resorption is the opposite of this; if apposition and resorption are in equilibrium, there is no change in bone volume. Augmentation and diminution are the flow of the alkaline earths to and from bone volume, respectively. They affect the density of the material in the bone and

thus affect the level of radioactivity at the site. Diminution produces a slow reduction in intensity throughout the bone. We can say that resorption reduces the volume of bone subject to radiation, while diminution reduces the dose in existing bone [20] (Figure 5).

In discussing isotope metabolism, these processes have to be taken into account along with the pathway by which the isotope is introduced. There are two major theoretical ways to consider isotope metabolism; in the first of these, the compartment model,[19] the transfer of substance from one part of the body to another is represented by the movement of material from one compartment to another. For example, the path of a material, such as radium, can then be traced from GI tract to blood to bone.[19]

Metabolic disorders of the bone may affect the metabolism of ^{226}Ra. While little is known about this, calcium metabolism is better understood and can be expected to be similar to that of ^{226}Ra. Among the factors which will affect body calcium are hyperparathyroidism, vitamin D excess, vitamin A poisoning, hyperthyroidism, Paget's disease and Addison's disease.

Radium levels in teeth appear to offer a possible indication of total radium exposure. To support this contention, Samuels has reported: 1) the uptake of radium into deciduous teeth (baby teeth) is proportional to radium exposure at the time of formation, 2) there is a very little turnover of radium, once acquistion has occurred, 3) there is a little uptake into formed teeth, and discrimination against radium. Other investigators[22] found that the radium variation in the skeleton is small, (>± 15% of the mean). However, it may be higher where the radium-calcium ratio is high and where radium levels in water are high.[23] Müller et al[24] examined a group of 52 persons who carried body burdens of strontium-90 varying from <0.2 to >2.2 μCi and ^{226}Ra varying from <0.1 to >1.0 μCi. There were no observed clinical changes in the group except for signs of radiation dermatitis. Karyological studies, (studies of the cell nucleus) of

bone marrow cells showed a statistically significant increase in the occurrence of aneuploid (having an abnormal number of chromosomes) cells as compared to healthy subjects. The study also suggests that a significant increase of chromosomal aberrations can be detected in patients with a ^{226}Ra body burden that is higher than 10 percent of the maximum permissible concentrat[illegible] (MPC). Tsai *et al*[25] found that ^{226}Ra irradiation altered the synthesis or breakdown of hexuronic acid and galactosamine (chondroitin sulfates). Since chondroitin sulfates play a role in the calcification process, this may be related to skeletal abnormalities.

The pathway for radium distribution is similar to that for calcium. Of the radium ingested, a portion is transferred to plasma, extracellular fluid and bone surfaces which make up the exchangeable pool, while the remainder is excreted directly. Of the radium in the pool, some is transferred to the bone, some is returned to the GI tract, while the remainder is excreted as sweat and urine (See Appendix C). However, Spencer *et al*[23] have observed distinct quantitative differences between ^{226}Ra and calcium metabolic behavior. Urinary excretion of ^{226}Ra was only 2.2 percent of total ^{226}Ra excretion, while urinary Ca excretion was 29 percent of total Ca excretion.

A second method of analysis postulates a retention function which describes mathematically the retention of a material by the whole body and various parts of it. These functions frequently have multiple terms indicating retention of a material for short and long times after injection. Marshall *et al*[26] have recently developed such a function that accurately reflects available data for radium.

The advantage of the compartment model is the ease of conceptualization - the transfer of ^{226}Ra between various parts of the body is clear. The retention function, however, provides for better quantification of isotope metabolism and thus allows for greater accuracy in prediction of isotope deposition. In both cases, there is a need for more accurate data as regards ^{226}Ra metabolism.

VII. HEALTH EFFECTS OF EXPOSURE TO ^{226}Ra

A. Animal Studies

Only a few of the available studies on the effects of ^{226}Ra on animals are especially useful in the consideration of low doses of ^{226}Ra. The limited usefulness of such studies is due to the small number of animals tested and single, high, or unknown doses used. Since the 1950's there have been three animal studies that do provide supportive data.[27,30] Two of these are long-term studies of the beagle dog carried out at the Universities of Utah[27,28] and California at Davis,[29,31] and the third is a long-term study of mice conducted at Argonne National Laboratory.[30]

In the Utah experiment, beagle dogs were administered a single intravenous injection of ^{226}Ra at the age of 18 months. These animals were called the Toxicity Animals, and they were maintained until their deaths. The doses given ranged from 0.000 to 10.4 μCi/kg animal weight. A second set of animals, the Test Animals, were given similar doses of ^{226}Ra and were then sacrificed as needed. Some animals in this group received the dose in six injections at 56-day intervals.

Among the Toxicity Animals, 32 out of 35 (given injections >1.07 μCi/kg) died with osteosarcoma, at an average of 4.65 years after injection. The other three animals died of distemper (one at 1.31 years, one at 1.34 years) or pyometritis (at 4.41 years). Of those receiving 0.062 - 0.339 μCi/kg (lower dose groups), 6 out of the 34 have died with osteosarcomas at an average of 10.44 years after injection. Among the test animals, osteosarcomas have occurred in the three highest dose groups.

The Davis study is also concerned with the toxicity of ^{226}Ra, in this case relative to that of ^{90}Sr. The dose levels ranged from 0.000 to 1.25 μCi/kg animal weight. The doses were given in eight equal semi-monthly installments beginning at 435 days of age. Fifteen osteosarcoma deaths (nine at 1.25 μCi/kg out of 38 dogs, six at 0.42 μCi/kg out of 41 dogs) have been reported.

Recently it has been reported that ^{226}Ra labeled humeri in beagles have shown bone damage for doses as low as 8 ng/kg body weight. This corresponds to a dose of 300 rad (cumulative) by 10 years of age.[32]

In the Argonne study, 3,210 female mice were administered a single injection of ^{226}Ra. The dose range for an initial group of 2,250 mice was 0.0-120.0 µCi/kg; a later group of 960 mice received doses of 0.0, 0.05, 0.10, 0.25 and 0.50 µCi/kg to cover lower levels not in the initial experiment. Osteosarcoma appeared at all levels; even at the 0.05 µCi/kg level. There was an observed increase over the controls, both of the number of mice dying with osteosarcoma and of the average number of tumors per mouse. The tumor expectancy (dose-response curve) increased rapidly in linear fashion from 0.0 to 2.5 µCi/kg and thereafter increased more slowly. This suggests that there are several mechanisms of oncogenesis.

B. Acute Exposure - Human

Several studies provide data on the carcinogenic effect from high doses of alpha emitting radionuclides deposited in human tissues. Linear extrapolation from the dose-effect relationships observed in these studies provide a basis to estimate the risk that may be associated with the low doses resulting from elevated radium in drinking water. Particularly relevant are the reports by Miller, Evans, Finkel, Goss, Sharpe, and Rowland[6,33-37] on neoplasms attributed to occupational and medical exposure to ^{226}Ra and the studies by Spiess and Mays[38] on neoplasms resulting from the intravenous injection of ^{224}Ra into humans. These studies clearly show that bone sarcomas and other malignant neoplasia are causally associated with high body burdens of radium radionuclides. The data from these human studies indicate a dose effect proportionality for the radiogenic induction of bone neoplasam when the total cumlative dose exceeds about one hundred rads. It is estimated from these studies that the risks

for malignant bone neoplasms are about one and five cases per million man-years per rad, following the initial exposure to ^{226}Ra and ^{224}Ra, respectively.[3]

Further analysis of the data of Spiess and Mays indicate that the incidence of bone sarcomas in the ^{224}Ra patients, in whom the total dosage was protracted over a 2 to 4 year period, was almost double that among those who received the same total dosage in less than a year.[38] These findings support the concept that the relative biological effectivness (RBE) increases as dose rate diminishes. The ^{224}Ra studies also provided some insight on age sensitivity. About one-fourth of the patients were juveniles, ranging in age from 1 to 20 years; they experienced almost twice the incidence of bone neoplasia per rad than the adults.

Other alpha emitting radionuclides that involve different tissues also have been shown to be effective carcinogens at relatively high dose levels. Patients injected with thorotrast have been followed for their cancer mortality experience.[39-42] Thorotrast is a colloidal suspension of dioxide of thorium, a long-lived alpha emitter that was widely used as an x-ray contrast medium during the 1930's. Thorium salts deposit in many tissues, but mainly in the bone and liver. One of the decay daughter products of thorium is radon-220, which is absorbed into blood and eventually exhaled, exposing the lungs to a continuous low level of alpha exposure. Statistically significant increases in respiratory cancers and a variety of malignant neoplasia of the liver, hematopoietic system and other tissues were reported among the thorotrast patients. The excess cancer risk associated with the alpha radiation doses from thorotrast ranged from 5 to 80 cases per rad per million man-years of exposure for different target organs.

Several studies have been carried out on the lung cancer mortality experience of men occupationally exposed to alpha emitting radionuclides of radon and radon daughters present in the air of "hard rock", especially uranium mines.[3,42,45] An

excess of bronchiogenic carcinoma has been attributed to this occupational exposure at a rate of about 5 excess cases per rad of alpha dose per million man-years.[3] In the study of uranium miners by Lundin *et al*,[42] the risk of respiratory cancer per unit of exposure was greater in the lower cumulative exposure groups than in the higher ones, again indicating an increase in RBE with decreasing dose or dose rate.

C. Chronic Exposure - Human

All the studies summarized above involved population groups exposed to cumulative alpha radiation doses, usually in excess of 100 rads. However, total cumulative doses from drinking water in the exposed population are on the order of 0.5 to 1.0 rad. An epidemiologic study of individuals exposed to elevated levels of ^{226}Ra in drinking water by Peterson *et al*[9] is the only reported attempt to measure health effects that may be associated with such low cumulative alpha doses. They found that the exposed population of one million people in 111 Illinois and Iowa towns had a bone neoplasm mortality rate of 1.41 deaths per 10^5 compared to $1.14/10^5$ in the control population ($p<0.08$) based on data derived from death certificates for the period 1950-62. The "exposed" and control groups had average concentrations of 4.7 and 0.1 pCi/liter ^{226}Ra in drinking water, respectively. One part of the evaluation examined the uptake of ^{226}Ra from public water supplies into deciduous teeth.[21] It was demonstrated that the uptake of radium into deciduous teeth is proportional to the chronic radium exposure during the time of formation of the teeth. It was also suggested that because placental transfer of radium has been demonstrated, the larger ingestion of ^{226}Ra in the maternal diet relative to the infant diet would lead to greater ^{226}Ra exposure *in utero* than *extra utero*.

The findings from the Peterson study are equivocal (not statistically significant at the 0.05 level) and should be interpreted with recognition of the limitations inherent in the

methodology and the marginal levels of the statistical reliability of the reported results. Nevertheless, the findings are fully consistent with the dose-effect relationship theory for high-LET radiation (discussed more fully below). In this study, it was also shown that an intermediate rate of 1.25 cancers/10^5 was exhibited by the population in Illinois and Iowa which was not included in either study group, but which was exposed to an average radium concentration higher than that in the control communities and lower than that in the exposed communities. This is suggestive of a proportional dose-effect relationship. Further, there was some evidence to suggest that the excess cancer rates were higher in the exposed population under 30 years of age than in the exposed group 30 years and over. Another significant finding related to the age specific mortality based on deaths from all causes. The exposed group from 0 to 9 years of age had a death rate from all causes of 3.45/10^5 compared to 3.16/10^5 in the control ($p < 0.03$). It should be noted, however, that Chicago also showed a higher bone neoplasm mortality rate than the control population. This could not be attributed to elevated radium exposure, since Chicago is served by a surface water supply having less than 0.1 pCi/liter ^{226}Ra.

The U.S. Environmental Protection Agency (EPA) recently promulgated new maximum contaminant levels for alpha radioactivity in drinking water of 5 pCi/liter for combined ^{226}Ra and ^{228}Ra, and 15 pCi/liter for gross alpha activity (including ^{226}Ra).[44] The new standards replace the present U. S. Public Health Service drinking water standards for radium of 3 pCi/liter.

Ingestion of 5 pCi of ^{226}Ra/liter of drinking water over a period of months would result in an equilibrium body burden of about 400 pCi in "Standard Adult Man" which is more than six times the body burden associated with the

usual human diet.[13] A body burden of 500 pCi of radiation would deliver a skeletal dose of approximately 15 millirad, or 150 millirem per year. The conversion of the "rad" to the "rem" unit is based on the use of a "relative biological effectiveness" (RBE) factor of 10 as recommended by the International Commission on Radiological Protection.[45] There is very little information available on the health effects in humans from such low dose rates of alpha radiation to tissue, with the possible exception of equivocal findings from the epidemiologic study by Peterson *et al*[9] which are discussed above. However, the risks associated with dose levels of the order of 150 millirem per year can be estimated by linear extrapolation from the dose effect relationship reported from studies of humans exposed to much higher doses and dose rates.[2,44] Based on linear extrapolation, 150 millirem per year would result in an excess of 0.7 to 3.0 cases of malignant tumors per year per million exposed persons. It is estimated that 60 to 85 percent would be malignant bone neoplasms.[7,44]

In using such LEMs (Linear Extrapolation Models) to estimate the risks that may be attributed to low doses of radiation, a distinction must be made between low-LET (Linear Energy Transfer) and high-LET radiations.[2,45-48] Linear Energy Transfer is the conventional expression that denotes the density of energy deposition along the track of an ionizing radiation particle or photon. Gamma rays, x-rays, and beta particles generate low-LET tracks, whereas radium and other natural sources of alpha particles result in high-LET tracks.

High-LET radiations per unit of radiation dose (i.e. rads) are much more effective than low-LET radiations in the induction of serious long term effects, such as malignant neoplasms. There is some evidence that the carcinogenic risk per unit of high-LET radiation dose does *not* appear to decrease, and in some instances appears to increase, with decreasing doses and dose rates for which the lower limits are not known.[3,44,46] Therefore, the use

of the LEMs to estimate the risks for low dose and low dose rates of high-LET radiation may actually underestimate the risks.

It is noteworthy to compare the excess malignant bone neoplasia that Peterson *et al*[9] found to be associated with radium in drinking water to the cancer risk predicted by a LEM.[2,7,45] Peterson *et al* reported an excess of about 30 deaths due to malignant bone neoplasms in the exposed group during the 13-year study period in contrast to the 5 to 28 malignant bone tumors that would be predicted by the LEM of National Academy of Sciences BEIR, Thus, the data of Peterson *et al* further suggest that the LEM does not overestimate and may actually underestimate the carcinogenic risk of low dose and low dose rates of high-LET radiation.

D. Non-Carcinogenic Effects of ^{226}Ra Exposure

Epidemiological studies reviewing the human radium experience are concerned primarily with bone sarcomas and carcinoma of the paranasal sinuses and mastoids.[27] Other disease conditions appear in these studies for which radium as the causal agent can neither be established nor denied. For example, in the Argonne National Laboratory series, four central nervous system tumors have been documented.[33] Many spontaneous fractures from varying degrees of radium deposition in the skeleton have been reported in both the ANL-ARCH series[33] and the MIT series.[6,49-51] Other possible adverse effects of ^{226}Ra include life-shortening, leukemia, mammary gland tumors and many other soft tissue tumors.[27] A higher than expected incidence of conduction, nerve, and mixed-pattern deafness may also be associated with exposure to ^{226}Ra.[37]

Moreover, for those people whose body burdens were above 0.6 μCi, jaw necrosis and fractures of long bones (especially through the femoral shaft) at a relatively early age were frequent occurrences.[36] For people with burdens above 1.0 μCi, carcinomas in the epithelium of the accessory sinuses behaved as radium-induced malignancies with a long latent period (30 or more years).[36] Sharpe also suggested that female, but not male, life

spans were shortened. The life shortening may be the result of a difference between men and women in age at first exposure to radium.[37] Teratogenic and mutagenic effects are caused by many emitting nuclei;[3] this suggests that exposure to ^{226}Ra may also cause these effects.

As indicated in Appendix A, radon-222, the daughter product of ^{226}Ra, is also radioactive, as are other nuclides in this decay chain. Most of them decay by the emission of α particles of energy on the order of 5 MeV. Thus, these nuclides too could have an effect on the health of those ingesting ^{226}Ra. The nature of this effect will depend on the metabolism of the various decay products; ^{222}Rn, for example, is a noble gas which may move to the lipids and central nervous system. Little is known about these effects.

E. Calculation of ^{226}Ra Body Content

The average content of ^{226}Ra in bone ash from 42 healthy individuals who lived all their lives in cities whose drinking water sources had less than 0.1 pCi ^{226}Ra per liter was 0.0124 pCi/g.[52] This corresponds to a whole skeletal content (2600g ash) of 0.32×10^{-10}g. In order to extrapolate from bone to whole body content, measurements of radium in soft tissue ash were found to be 0.8 that of bone ash (for equal weights of bone and soft tissue ash). Since the skeleton constitutes 86 percent of the whole-body ash, only 10 percent to 15 percent of the radium is found in the soft tissues, and the average radium content of soft tissues is 0.04×10^{-10}g (12.5 percent total). Adding this to the 0.32×10^{-10}g found for the skeleton gives a whole-body content (Standard Man: 3000g ash) of 0.36×10^{-10}g. Since the ^{226}Ra concentration in the drinking water was very low, 0.36×10^{-10}g of ^{226}Ra represents the relative contribution food makes to the radium body burden. From an earlier experiment, Stehney and Lucas[53] determined the daily intake rate for humans in Chicago, Illinois to be 1.6 pCi/day. Thus, the whole-body

content of 0.36 X 10^{-10} g corresponds to 22 times the daily intake.

Lucas also made measurements on a total of 35 bones from 34 people (ages from 0 to 84 years) who lived all their lives, or not less than the last 30 years, in a city with high radium drinking water (range was from 0.13 to 10.5 pCi/liter ^{226}Ra).[1] The radium content varied from 0.012 pCi/g ash for a resident of a city with 0.13 pCi/liter in the drinking water to a high of 0.47 pCi/g ash in a city with 10 pCi/liter of water. Lucas found an excellent correlation of ^{226}Ra radium in bone with that of the intake of water which contained more than 1 pCi/liter. The average ^{226}Ra body content for a Standard Man who drinks water containing more than 0.1 pCi ^{226}Ra/liter would then be approximately equal to the amount of ^{226}Ra found in 50 liters of that water. For less than 1 pCi ^{226}Ra/liter, normal statistical variations from food uptake overlap the uptake from water.

Thus, for drinking water containing 5 pCi ^{226}Ra/liter, the whole-body content of radium from water would equal 5 pCi/liter times 50 liters, or 250 pCi for Reference Man. If the whole-body content of radium from food (0.12 pCi/g X 3000g = 36 pCi) is added, a total whole-body content of radium of 286 pCi is obtained.

VIII. POPULATIONS AT RISK

A. Age as a Sensitivity Factor

Cells that display the greatest sensitivity (i.e., disruption of metabolic activity) to ionizing radiation are generally those which are in a relatively active process of either division, differentiation or growth.[54,55] Thus, radiosensitivity is dependent on age, with fetuses, newborns and children being at a higher risk than are adults.

Spiess and Mays,[38] in their study of ^{224}Ra patients, report that the effectiveness per rad for alpha emitters is higher with longer protraction of dose and that juveniles are more sensitive by a factor of over 50 percent. (See "Effects of ^{226}Ra on Human:

Acute Exposure"). The Peterson study of chronic effects of continuous, low level exposure to ^{226}Ra suggested that excess cancer rates were higher in the exposed population under 30 years of age than in the exposed group 30 years and over ($p<0.10$).[9]

Further evidence implying that intrauterine and neonatal animals are more susceptible than adults to ionizing radiation is based on observations of placental transfer and of specific organ or tissue damage by single or discontinuous doses.[54-57] Einck-Rosskamp *et al*[58] found cross-placental transfer of ^{228}Ra in pregnant rabbits injected with 50 ml thorotrast (50 percent ^{228}Ra and ^{228}Th with their daughters) at different times, before and after copulation. The rabbits were sacrificed at different times of pregnancy and the fetuses, placentas, blood and several organs of dams were analyzed for ^{232}Th daughters. Approximately 0.01 percent of the injected activity could be detected in the tissues.[56] It was found that the developing fetuses accumulated more radium than the dam's muscle tissue.

B. Enzyme Deficiencies

Taylor *et al*[57] first suggested that catalase might be able to modify the effects of ionizing radiation. Since ionizing radiation is known to affect the production of peroxides such as H_2O_2 in tissue, and since catalase is known to detoxify H_2O_2, it is reasonable to hypothesize that catalase may have a modifying effect on the action of radiation on the body.[60] Experiments by Evans[41] supported the hypothesis of Taylor *et al* when he demonstrated that crude extracts of sea urchin sperm containing catalase could prevent death of sperm immersed in irradiated sea water. Barron and Dickman[61] showed that the addition of catalase (0.3 g/milliliter) partially prevented the inaction of crystalline phosphoglyceraldehyde dehydrogenase by both α and β-radiation. They indicated that H_2O_2 contributed about 30 percent of the total inhibition caused by α-radiation and somewhat more for inhibition by β-rays.

A Swiss study utilizing acatalasemic human subjects found that red blood cells from acatalasemic people, when exposed to irradiation, form methemoglobin (MetHb) about 10 to 20 times faster than "normals".[58] Furthermore, the effect of X-irradiation on cancer cells is tremendously reduced by simply adding catalase to the outside of the cell.

Catalase has been found to be present in both the nucleus and cytoplasm. However, it seems that about 90 percent of the catalase is apparently present in the cytoplasm.[59,60] The location of catalase within the cell is considered important with respect to the metabolism of its substrate (H_2O_2).[59] Consequently, cytoplasmic catalase may protect against the formation of MetHb and/or changes in cell membranes, while nuclear catalase is thought to offer limited protection to the DNA from H_2O_2. Since only a small percentage of catalase is present in the nucleus, it seems that catalase may not be highly effective in protecting the genetic material from oxidant stress. However, since the volume of the nucleus compared to the entire volume of the cell is often quite small, there may not be the low levels of catalase in the nucleus as compared to levels in the cytoplasm, if viewed on a per volume basis.

It has been found that catalase actually plays a secondary role to glutathione peroxidase (GSH-Px) in the detoxification of H_2O_2 and, in fact, only when the concentration of H_2O_2 exceeds a certain undefined high level does catalase serve a significant role in H_2O_2 detoxification. This finding may help to explain the widespread conflicting reports concerning the protective effects of catalase on ionizing radiation. For example, in contrast to previous reports indicating the importance of catalase with regard to detoxifying H_2O_2 following irradiation, a study with hypocatalasemic guinea pigs exposed to various levels of irradiation was not significantly different from the controls with regard to radiation sensitivity and longevity.[63]

The dose of radiation which produces the "critical"

concentration is probably modified by several factors, including natural levels of catalase in the various tissues (levels are specific for each tissue) and serum vitamin E, which is associated with the accumulation of peroxides and selenium (Se) levels.[61]

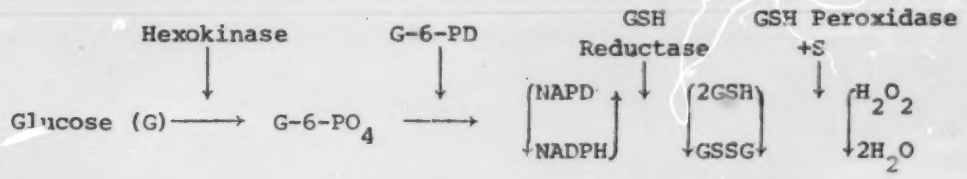


Figure 6: Biochemical Scheme by Which Glutathione Peroxidase Detoxifies H_2O_2

However, the principal way in which the cell detoxifies H_2O_2 (reduces oxidant stress) is by the action of the GSH-Px. Figure 6 shows the relationship of GSH-Px in its normal biochemical scheme. Thus, in order to maintain continuous functioning of this enzyme, it is necessary to continuously form reduced GSH, which in turn is dependent on other factors, such as the supply of glucose, the enzyme G-6 PD to reduce NADP to NADPH, and GSSG reductase. In support of this description, human studies (*in vitro*) on the effects of peroxide on normal cells, acatalasemic cells and cells deficient in G-6-PD, indicated that only cells deficient in the G-6-PD enzyme showed marked increases in reduced GSH levels.[62] It should be emphasized that such changes are closely associated with increased cell membrane fragility. Based on gene frequency determinations the number of individuals with acatalasemia and G-6-PD deficiency in Illinois is estimated to be approximately 40,000 and 200,000, respectively.[61]

Other groups at high risk may be those with metabolic bone disorders which may affect ^{226}Ra uptake. The type of disorder is indicated in Section V. C: Metabolism.

IX. APPENDICES

Appendix A - Physical Properties

According to the laws of quantum mechanics, electromagnetic radiation can be considered to have both wave and particle characteristics. Thus, particles, such as electrons [β (beta) particles], protons, neutrons and helium nuclei [^4_2He, α (alpha) particles] will follow Planck's law:

$$E = h\nu \qquad (A1)$$

with E = energy, (ergs) h = Planck's constant (6.6256×10^{-27} erg sec.) and ν = frequency, (Hz).

In order to apply this law an effective wavelength and frequency for each particle must be determined. This is given by De Broglie's law

$$\lambda = \frac{h}{p} \text{ or } \nu = \frac{pc}{h} \qquad (A2)$$

with λ = wavelength, c = speed of light (3.0×10^{10} cm/sec), and p = momentum = Mv (mass times velocity) of the particle. From this we can determine the spectrum of electromagnetic radiation:

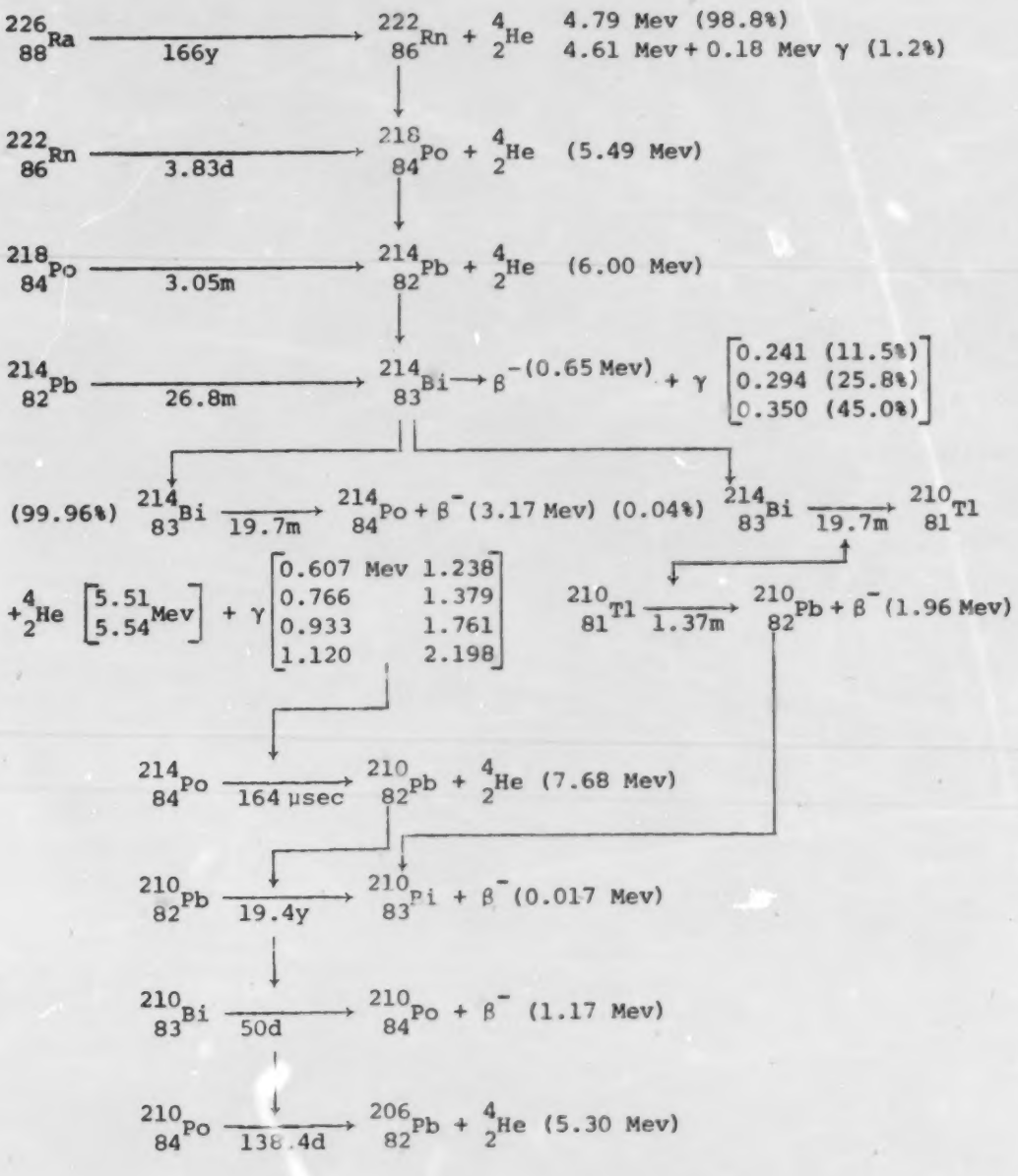
Name	Radio	Infrared	Visible	Ultraviolet
Wavelength (cm.)	>1	10^{-4}	5×10^{-5}	10^{-5}
Energy (erg.)	$<2.0 \times 10^{-16}$	2×10^{-12}	4×10^{-10}	2×10^{-11}
Energy (Mev)	4.25×10^{-10}	1.25×10^{-6}		1.25×10^{-6}

Name	X-ray	γ Ray	β	α
Wavelength (cm.)	10^{-6}	10^{-7}	1.25×10^{-20}	2.6×10^{-11}
Energy (erg.)	2×10^{-10}	2×10^{-9}	1.6×10^{-6}	1.6×10^{-6}
Energy (Mev)	1.25×10^{-10}	1.25×10^{-3}	1.0	4.75

One may obtain the wavelengths and energies for the α and β particles by taking E_α = 4.75 Mev and E_β = 1.0 Mev which are in the range of energies for these particles in the decay of ^{226}Ra.

The law of conservation of energy indicates that energy can neither be created nor destroyed; however, it can be transformed. In the decay of a nucleus, mass energy and nuclear energy (which holds the nucleus together) are being transformed into the kinetic energy of the α and β particles given off, and into electromagnetic energy of γ rays. Another energy transformation takes place when these particles collide with atoms (for example in a cell). Some of the α, β, and γ rays' energy may be transferred to the atom. Within the atom electrons move in orbits around the nucleus; when they absorb energy they will be excited to a higher orbit or they will escape the atom. In the latter case the atom is said to be ionized. Each electron can absorb only certain specific amounts of energy, depending on its orbit in the atom and on the type of atom. For an electron near the nucleus of an atom, much energy is needed to remove the electron from the atom; for example, 70,000 ev are needed to remove a K electron from the tungsten atom. For an electron further from the nucleus or for a lighter atom, less energy is needed for ionization; thus, for an electron in the ground state for hydrogen, only 13.6 ev are needed for ionization. Thus, radiation of a wide range of energies can be ionizing radiation. α, β, and γ rays (all high energy) can ionize many substances like water, oxygen, and so on.

Along with the ionization process we must also consider the process of radioactive decay. In general, there are three main routes for decay of an unstable nucleus: the emission of an α particle (^4_2He), the emission of a β particle (either β^+ or β^-), or the emission of a γ ray. For ^{226}Ra, a part of of the ^{238}U series, the first step in the decay chain is the disintegration of ^{226}Ra into ^{222}Rn with the emission of an α particle. The chain is shown on the following page.[18]



y = years

d = days

m = minutes

s = seconds

Figures in parentheses and brackets indicate the energy of the particles and the percentages in which the alternative reactions occur at each step. Numbers under the arrows give the half-life for the reaction. The half-life is the time in which half of the nuclei originally present decay to the daughter product. Note that there are two branches to the chain at step five which re-combine at step seven.

The half-life (T) of an atom is defined above; the decay constant λ is related to the half-life by $\lambda = 0.693/T$ (this should *not* be confused with wavelength λ). The average life ($\bar{T} = 1.443T$) is the mean life span of all radioactive atoms. The activity of a sample of a radioisotope is defined as the number of atoms disintegrating per second. If there were originally N_0 atoms present, then at time t there will be N_1 atoms present with

$$N_1 = N_o\, e^{-\lambda t} \qquad \text{(A 3)}$$

and the activity will be λN_1.[19] Activity is usually given in curies, with one curie (Ci) = 3.7×10^{10} disintegrations per sec (dis/sec). Since there are, for any isotope,

$\frac{\text{A gm/male}}{6.025 \times 10^{23}\ \text{atoms/male}}$ with 6.025×10^{23} = Avogadro's number and A = the isotopic weight, then for an atom with isotopic weight A and decay constant λ, the mass of one curie = $\frac{3.7 \times 10^{10}}{\lambda} \cdot \frac{A}{6.025 \times 10^{23}} = 6.14 \times 10^{-13} \frac{A}{\lambda}$ gm. For ^{226}Ra there are 1.03 grams per curie.

The number of atoms, dN, disintegrating in time dt is proportional to the number of atoms present (that is, $dN = d\lambda\, dt$).[19] We can, for any radioactive atom, integrate this to determine the number of atoms (N) present at time t as a function of decay constant λ, and original number of atoms, N_0:

$$N = N_0\, e^{-\lambda t} \qquad \text{(Cf A 3)}$$

In the case of a series of decays (for example, ^{226}Ra) the number atoms N of successive daughter products depends on the original amount of

^{226}Ra present, since the disintegration of ^{226}Ra provides new ^{222}Rn, which is itself decaying (and similarly for other products).

Let us define:

N_0 = Number atoms of original material at t = 0 (in this case, ^{226}Ra)

λ_1 = Decay constant of original material (^{226}Ra)

N_1 = Number atoms of original material at time t (^{226}Ra)

N_2 = Number of atoms of 1st daughter material at time t (^{222}Rn)

λ_2 = Decay constant of 1st daughter (^{222}Rn)

N_3 = Number atoms of 2nd daughter at t (^{218}Po)

λ_3 = Decay constant of 2nd daughter product at time t (^{218}Po)

N_4 = Number atoms of 3rd daughter product at time t (^{214}Pb)

λ_4 = Decay constant of 3rd daughter product at time t (^{214}Pb)

We could continue and define $N_{v,\,6,\,7}$ for successive daughter products. Using the above definitions, we find that the number of each type of atom present at time t is:

$$N_1 = N_0\, e^{-\lambda,t} \tag{A.4}$$

$$N_2 = N_0 \frac{\lambda_1}{\lambda_2 - \lambda_1} \left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \tag{A.5}$$

$$N_3 = \frac{N_0\, \lambda_2\, \lambda_1}{\lambda_2 - \lambda_1} \left[\frac{(e^{-\lambda_1 t} - e^{-\lambda_3 t})}{\lambda_3 - \lambda_1} - \frac{e^{-\lambda_2 t} - e^{-\lambda_3 t})}{\lambda_3 - \lambda_2}\right. \tag{A.6}$$

$$N_4 = \frac{N_0\, \lambda_3\, \lambda_2\, \lambda_1}{\lambda_2 - \lambda_1} \left[\frac{1}{\lambda_3 - \lambda_1} \frac{(e^{-\lambda_1 t} - e^{-\lambda_4 t}}{\lambda_4 - \lambda_1} - \right.$$

$$\frac{e^{-\lambda_3 t} - e^{-\lambda_4 t})}{\lambda_4 - \lambda_3} - \frac{1}{\lambda_3 - \lambda_2} \frac{(e^{-\lambda_2 t} - e^{-\lambda_4 t}}{\lambda_4 - \lambda_2}$$

$$\left. - \frac{e^{-\lambda_3 t} - e^{-\lambda_4 t})}{\lambda_4 - \lambda_3}\right] \tag{A.7}$$

For successive products (N_n, λ_n) there will be a complicated series of exponentials with 2^{n-1} terms of the form:

$$N_n = \frac{N_0 \lambda_{n-1} \lambda_{n-2} \ldots \lambda_1}{\lambda_2 - \lambda_1} \left[\frac{e^{-\lambda_1 t} - e^{-\lambda_n t}}{(\lambda_3 - \lambda_1) \ldots (\lambda_n - \lambda_1)} + \ldots \right] \tag{A.8}$$

For the disintegration of ^{226}Ra, we are concerned primarily with the first two steps (Eq. 4 and 5). Since the half-life of ^{226}Ra is 1622 years and that of ^{222}Rn is 3.83 days, we have $\lambda_2 >> \lambda_1$ and thus Eq. 5 becomes

$$N_2 = \frac{\lambda_1}{\lambda_2} N_0 (1 - e^{-\lambda_2 t}) \tag{A.9}$$

Equation 6 gives $N_3 = 0$ since $\lambda_3/\lambda_2 >> 1$. The same will be true for succeeding products up to N_7 (^{210}Pb). ^{210}Pb has a half-life of nineteen years, and we will have for it:

$$N_7 = \frac{N_0 \lambda_1}{\lambda_7} (1 - e^{-\lambda_7 t}) \tag{A.10}$$

If we have a closed system where none of the atoms can escape, then after awhile, radioactive equilibrium will be established. At first, we will have only ^{226}Ra which will decay into ^{222}Rn. The number of atoms of ^{222}Rn will increase as the ^{226}Ra decays (at rate $N_1\lambda_1$). However, the ^{222}Rn will also decay at a rate of $\lambda_2 N_2$; eventually, the rate of increase and the rate of decay will become equal ($\lambda_1 N_1$) = ($\lambda_2 N_2$). The same will be true for other daughter products, and we will have: [18]

$$N_1\lambda_1 = N_2\lambda_2 = \ldots = N_n\lambda_n \tag{A.11}$$

For atoms with a short half-life, the number present will be small. We can see this from Eq. 5, for example. Since $N_1 = N_0 e^{-\lambda_1 t}$ and since $e^{-\lambda_1 t} > e^{-\lambda_2 t}$, we have:

$$-\lambda_1 t - e^{-\lambda_2 t} \simeq e^{-\lambda_1 t} \tag{A.4a}$$

$$\lambda_2 - \lambda_1 \simeq \lambda_2 \tag{A.4b}$$

and thus, $$N_2 \simeq \frac{\lambda_1}{\lambda_2} N_0 e^{-\lambda_1 t} \tag{A.4c}$$

or $$N_2 \lambda_2 \simeq \lambda_1 N_1 \tag{A.4d}$$

Energy is thus given off at each step of the decay process, with most of it in the form of α particles. This energy is then transferred to molecules and cells causing various biological effects.

TABLE A1

HALF-LIVES OF SOME α -EMITTING RADIONUCLIDES

ELEMENT	SYMBOL	HALF-LIFE
Americium	$^{241}_{95}Am$	458 y
Plutonium	$^{242}_{94}Pu$	3.79×10^5 y
	$^{240}_{94}Pu$	6580 y
	$^{239}_{94}Pu$	2.4×10^4 y
Neptunium	$^{237}_{93}Np$	2.14×10^6 y
Uranium	$^{238}_{92}U$	4.51×10^9 y
	$^{235}_{92}U$	7.13×10^8 y
	$^{234}_{92}U$	2.47×10^5 y
	$^{233}_{92}U$	1.62×10^5 y
Protactinium	$^{231}_{91}Pa$	3.25×10^4 y
Thorium	$^{232}_{90}Th$	1.41×10^{10} y
	$^{229}_{90}Th$	7340 y
	$^{228}_{90}Th$	1.913 y
Actinium	$^{225}_{89}Ac$	10.0 d
Radium	$^{226}_{88}Ra$	1622 y
	$^{224}_{88}Ra$	3.64 d
	$^{223}_{88}Ra$	11.43 d
	$^{222}_{88}Ra$	38 s
Francium	$^{229}_{87}Fr$	4.8 m

TABLE A1 (continued)

ELEMENT	SYMBOL	HALF-LIFE
Radon	$^{222}_{86}Rn$	3.823 d
	$^{221}_{86}Rn$	25 m
	$^{220}_{86}Rn$	55 s
Astatine	$^{217}_{85}At$	0.032 s
Polonium	$^{218}_{84}Po$	3.05 m
	$^{216}_{84}Po$	0.15 s
Bismuth	$^{214}_{83}Bi$	19.7 m
	$^{212}_{83}Bi$	60.6 m
Lead	$^{210}_{82}Pb$	21 y
Mercury	$^{187}_{80}Hg$	~3 m
Gold	$^{185}_{79}Au$	7 m
Platinum	$^{192}_{78}Pt$	10^{15} y
Holmium	$^{151}_{67}Ho$	42 s
Dysprosium	$^{154}_{66}Dy$	10^{6} y
Terbium	$^{151}_{65}Tb$	18 h
Gadolinium	$^{152}_{64}Gd$	1.1×10^{14} y
Samarium	$^{147}_{62}Sm$	1.06×10^{11} y
Neodymium	$^{144}_{60}Nd$	$\sim 5 \times 10^{15}$ y
Boron	$^{12}_{5}B$	0.02 s
Beryllium	$^{8}_{1}Be$	2×10^{-16} s

TABLE A2

RADIUM-226 STANDARDS

STANDARD	ROUTE OF INTAKE/SOURCE	GROUP EXPOSED	AGENCY
2.4×10^{-2} µCi/quarter	Oral	Occupational Exposure	NCRP
1.8×10^{-2} µCi/quarter	Inhalation	Occupational Exposure	NCRP
5×10^{-6} µCi/liter	Drinking Water	General Population	USEPA
3×10^{-6} µCi/liter	Drinking Water	General Population	USPHS
4×10^{-7} µCi/liter	Oral	Radiation Workers for 40-hour week	MPC - ICRP
3×10^{-11} µCi/cc	Inhalation	Radiation Workers for 40-hour week	MPC - ICRP

Appendix B - Biological Effects

The transfer of energy along the path of the particle is called the linear energy transfer (LET), and is measured in million electron volts per centimeter (Mev/cm). For an alpha particle, the LET value is high (i.e. it imparts large amounts of energy along its path), but the energy deposition is partially discontinuous. One can also define "relative biological effectiveness" (RBE) of different types of radiation as the inverse ratio of the doses in rads of two radiations required to produce the same biological effects.

The BEIR Committee Report and the NCRP Reports, numbers 39 and 43, generally characterize low-LET radiation as (a) before becoming exponential, the experimental dose-survival curve for cells has a "shoulder" which implies an accumulation of sublethal damage; (b) partial repair of cellular damage is demonstrated by the reappearance of a "shoulder" on the exponential part of the dose-survival curve when a second series of doses is given several hours after an initial exposure; (c) because of recovery of cellular damage, a higher dose is required to yield the same degree of the same biological effect, thus demonstrating a marked dose-rate dependence of effect; (d) the degree of effect is highly dependent on ambient conditions such as oxygen tension.[2,58,63]

High-LET radiations induce responses that are generally characterized as follows: (a) a smaller absorbed dose is usually required for a given degree of effect; (b) little or no recovery from damage is implied because the dose-survival curve is exponential; (c) a lack of repair of sub-lethal damage is demonstrated by the fact that fractionation alters very little the shape of the dose-effect curve; (d) little or no dose-rate dependence of degree is seen; (e) the degree of effect is minimally dependent on ambient conditions like oxygen tension.

We shall look further at some of the specific changes that a radiation in particular can effect in its passage through the cell. Radiation can have several effects on the cell. One of these is its

effect on the water molecules. The radiation will ionize the water molecule; an electron will be released and will be trapped or solvated by other water molecules due to their polarity:

$$H_2O \xrightarrow{h\nu} H_2O^+ + e^- \qquad \text{(B 1)}$$

The ionized water molecule breaks up into a hydrogen ion and an hydroxyl radical with an unpaired electron:

$$H_2O^+ \longrightarrow OH + H^+ \qquad \text{(B 2)}$$

Alternatively, the radiation may excite the water molecule which will break up into a hydrogen atom with an unpaired electron and an hydroxyl radical:

$$H_2O \xrightarrow{h\nu} H_2O^* \longrightarrow H\cdot + \cdot OH \qquad \text{(B 3)}$$

The $\cdot OH$, $H\cdot$, and e^- can then undergo chemical reactions like

$$\cdot OH + \cdot OH \longrightarrow H_2O_2 \qquad \text{(B 4)}$$

H_2O_2 is hydrogen peroxide, a strong oxidizing agent.[18] Another reaction is:

$$H\cdot + H\cdot \longrightarrow H_2 \qquad \text{(B 5)}$$

This is a hydrogen gas molecule. If the oxygen is in the tissue, it can combine with the hydrogen to form the hydroperoxyl radical which further combines to form more hydrogen peroxide (See Figure B 1, *pg. 50*).

$$H\cdot + O_2 \longrightarrow HO_2 \qquad \text{(B 6)}$$

$$H\cdot + HO_2 \longrightarrow H_2O_2 \qquad \text{(B 7)}$$

These compounds can lead to the detachment of amine groups from amino acids, removal of carboxyl groups from organic acids, oxidizing sulfhydryl (SH) compounds and decomposing simple sugars, such as glucose. The solvated electrons, H· and ·OH may also attack the pyrimidine bases (thymine, uracil, cytosine) of DNA and RNA. (Figure B 2) Each of these bases is a hexagonal ring compound with two nitrogens and a double bond between the fifth and sixth carbon atoms. This double bond is attacked, producing radical intermediates which have an unpaired electron at the five positions. These will pick up H· and ·OH radicals to form relatively stable end products. This is likely to cause genetic mutations which affect the coding of the DNA and RNA, leading to the production of altered protein. The alpha particle in particular can also attack the DNA directly.[18]

Consider the survival functions for entities (i.e., cells, molecules, viruses, etc.) that are irradiated.[19] N biological entities are irradiated; of these, dN are inactivated. The number inactivated is proportional to the dose, dD and the number initially present:

$$dN = - \frac{1}{D_0} N_0 dD \qquad \text{(B 8)}$$

D_0 is a proportionality constant; it is the dose required to inactivate all entities if they continued to be inactivated at the initial rate. D_0 is the mean lethal dose. Integrate Eq. 19 to obtain:

$$N = N_0 e^{-D/D_0} \qquad \text{(B 9)}$$

Thus, when $D = D_0$, $N = .37 N_0$. This equation applies only to small increments in the dose and is based on the assumption that a single hit will inactivate the entity. However, it may be that there are n sensitive areas that must be hit before the entity is inactivated. In that case the survival curve is given by:

$$\frac{N}{N_O} = 1 - (1 - e^{-D/D_O})^n \qquad \text{(B 10)}$$

For doses large compared to D_O, this reduces to:

$$N = N_O\, n\, e^{-D/D_O} \qquad \text{(B 11)}$$

This curve, as well as that given by Eq. B 9, will be straight lines which, when extrapolated back to D = O, will intercept the y axis (N) at N = n (See Figure B 3). The curve at small doses will follow Eq. B 10 and give a shoulder.[18]

The mean lethal dose, D_O, is also related to the target size. If V = volume of the target (cuμ), ρ = density of volume, W_O = energy in volume required to deactivate it (*i.e.*, the energy required to produce one ion cluster), then

$$V = \frac{9.016 W_O}{D_O\, \rho} \text{ cuμ} \qquad \text{(B 12)}$$

so that D_O is inversely proportional to target size. Thus the smaller the target, the more difficult it is to hit, and thus the larger the dose required to inactivate it.[18]

Different types of cells react differently to radiation and each cell will vary in its reaction depending on its position in the cell cycle. This is illustrated in Figures B 4, a and b. It is believed that the Chinese hamster cell reaction is more typical of an average cell than in mouse L.[18]

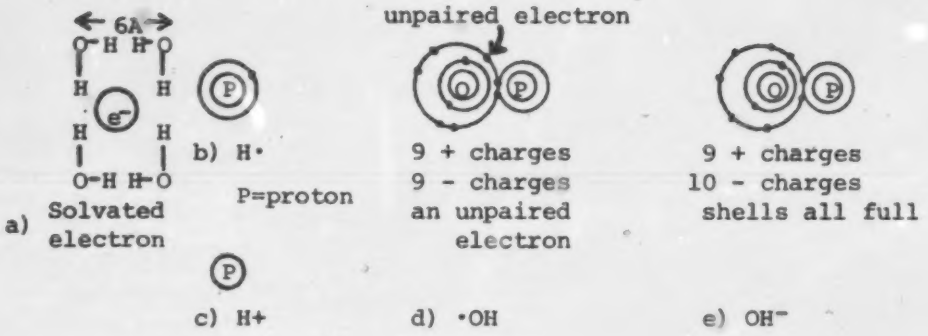
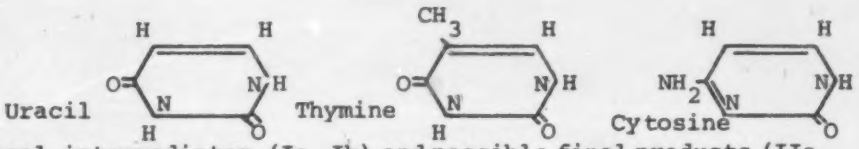


Figure B1: Nature of reactive species produced in water by ionizing radiations - a) Aqueous electron or solvated electron; b) Hydrogen radical; c) Hydrogen ion; d) Hydroxyl radical; e) Hydroxyl ion.[19]

a) bases in DNA and RNA



b) radical intermediates (Ia, Ib) and possible final products (IIa, IIIa, IIb, IIIb)

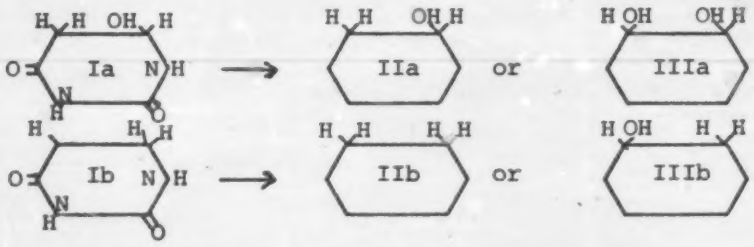


Figure B2: a) Structure of the three pyrimidines - uracil, thymine, and cytosine. b) Nature of intermediate radicals and final radiation products produced when e⁻, •OH, and H• attack uracil.[18]

Figure B3: Survival Curves for Hamster Fibroblast Cells[18]

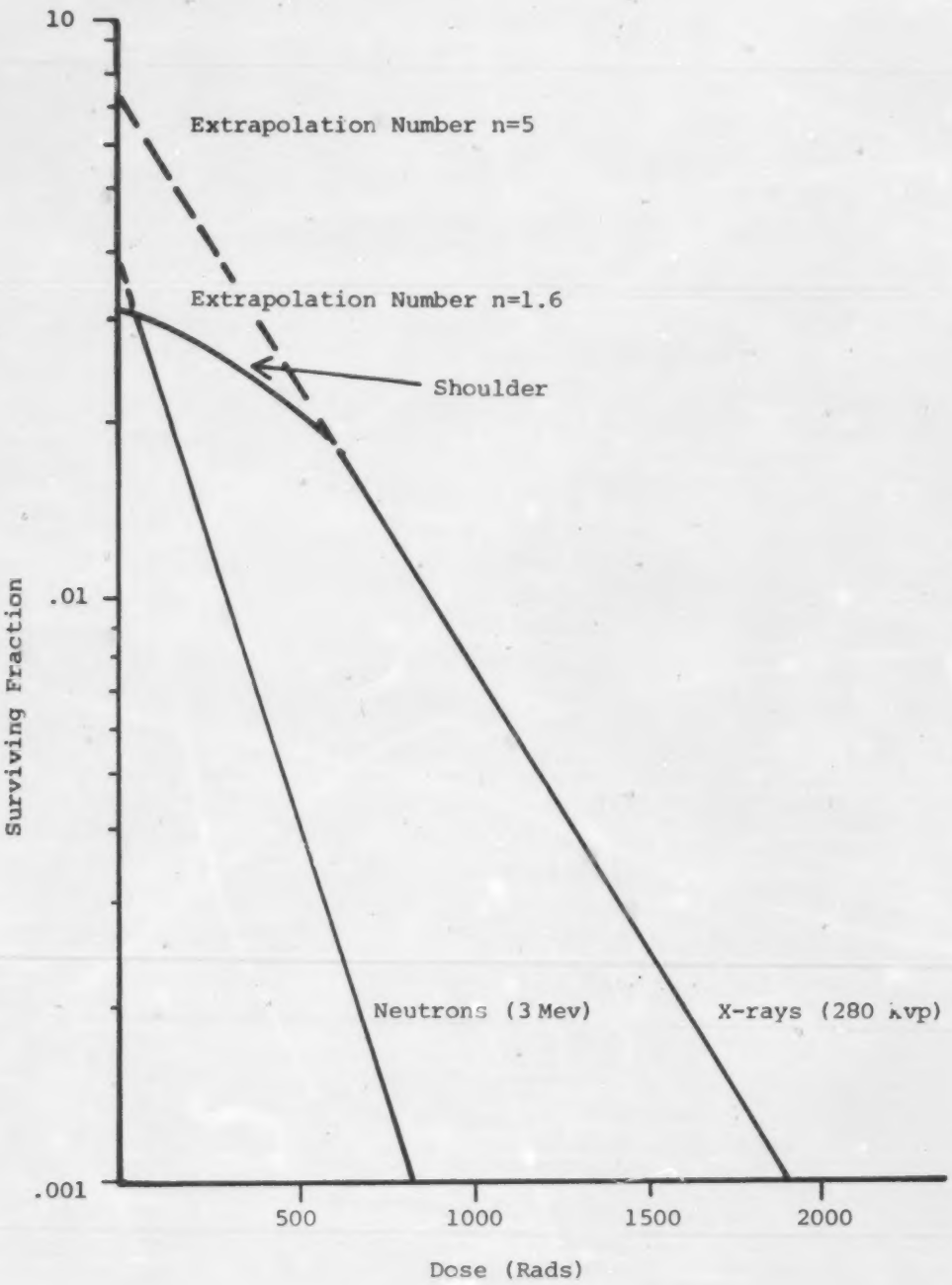


Figure B4a: Survival Curves for Mouse L Cells in Different Parts of the Cell Cycle (250 kvp X-rays)[18]

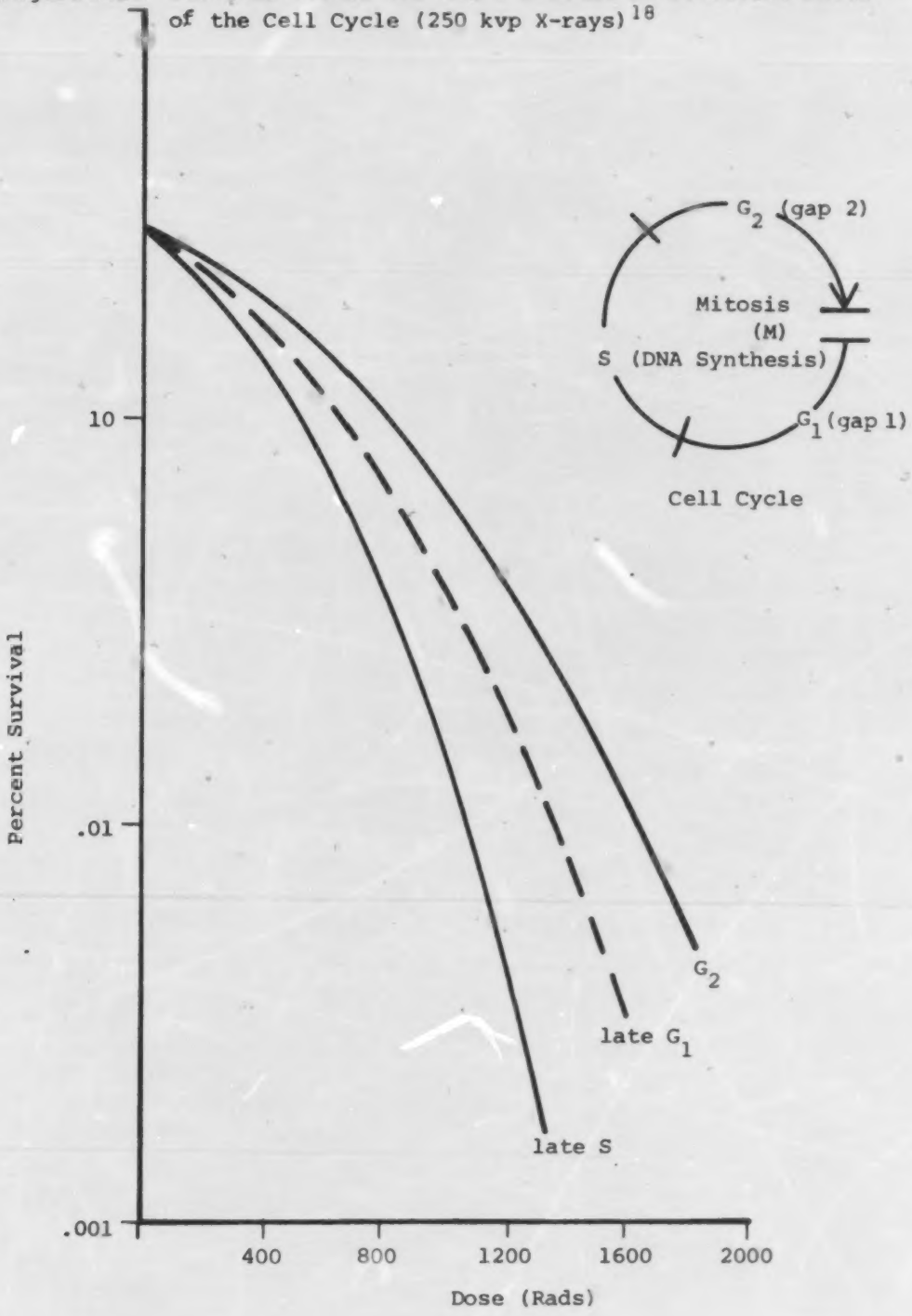
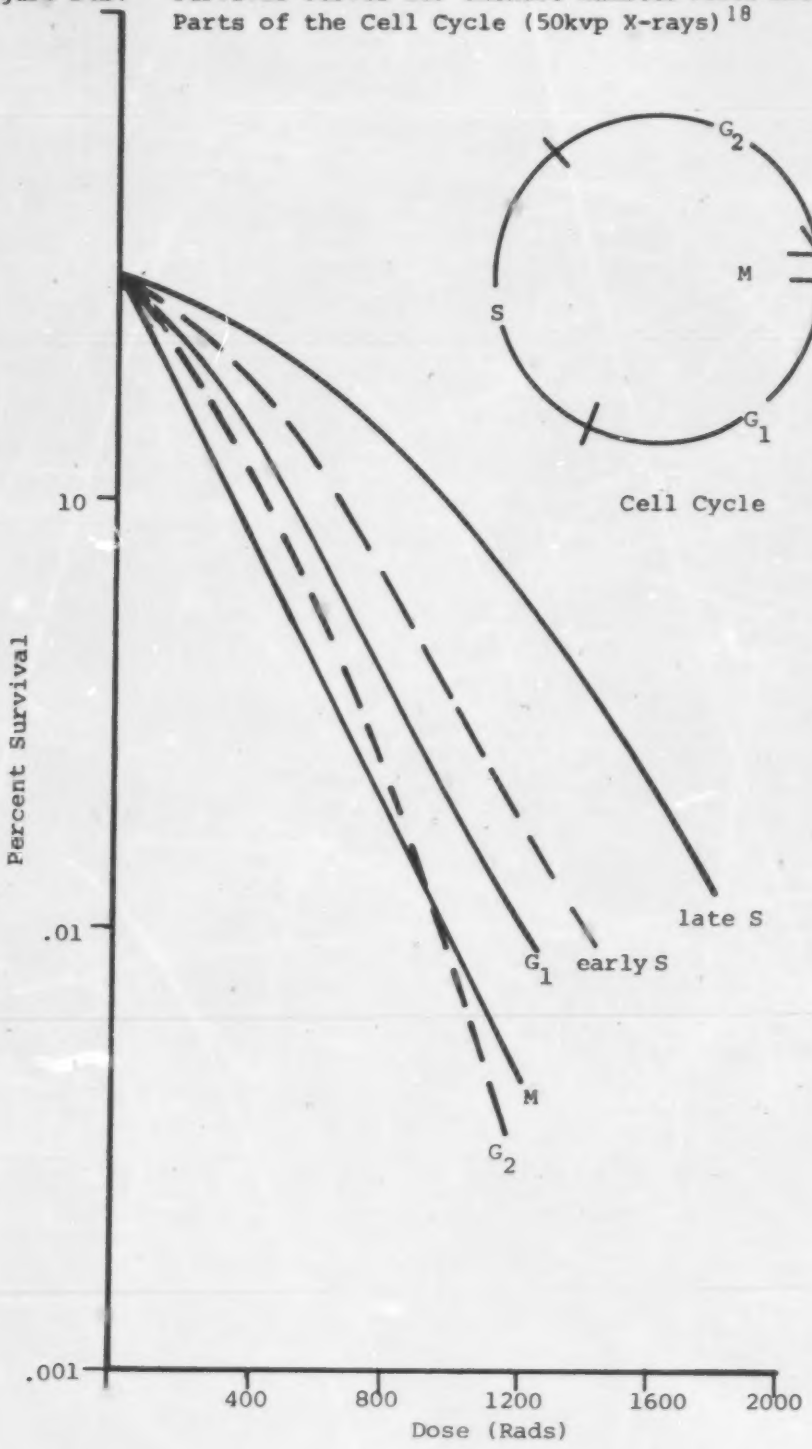


Figure B4b: Survival Curves for Chinese Hamster Cells in Differen Parts of the Cell Cycle (50kvp X-rays)[18]



Appendix C - Metabolism

Metabolism can be considered from both theoretical and experimental viewpoints. By developing a theoretical model for radium retention and uptake, predictions can be made about the distribution of ^{226}Ra in the body and thus about its biological effects. Two major theoretical approaches have been developed. The first of these is the compartment model.[18] In this model the transfer of a substance from one part of the body to another is represented by the movement of material from one compartment to another. In this model it is assumed that the system is in dynamic equilibrium - that is, the number of atoms (M) of the stable element, *e.g.* Ca, is constant and thus the number of atoms entering (m) is the same as the number leaving. If a number of atoms (x) of a radioactive element are added and these atoms mix rapidly with the stable element, the radioactive atoms will soon leave at the same rate as the stable ones. If dx/dt is considered the rate at which radioactive atoms leave, then:

$$\frac{dx}{dt} = \frac{m}{-xM} = -xK \qquad \text{(C 1)}$$

Using this, one can analyze models for the transfer of radioactive atoms. Two examples follow. The simplest situation is that of a single compartment into which are introduced radioactive atoms with Q_0 activity at time t = 0. Q is the activity in the compartment at time t, K is the turnover rate, defined above, and λ is the physical decay constant. Then:

$$\frac{dQ}{dt} = -(\lambda + K)Q \qquad \text{(C 2)}$$

Integrating, one obtains (See Figure C 1a):

$$Q = Q_0 e^{-(\lambda + K)t} \qquad \text{(C 3)}$$

Figure C1: Compartment models: a) single compartment, b) two compartments with back-flow.[18]

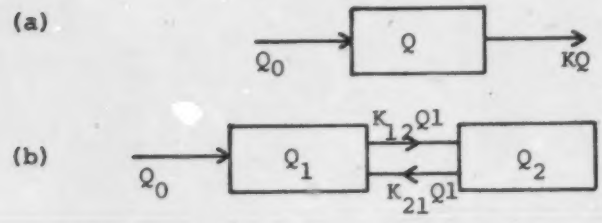


Figure C2: Model for Radium Distribution

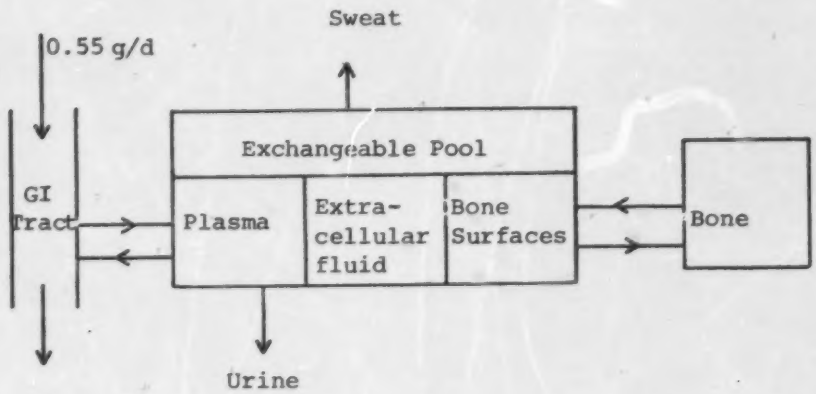
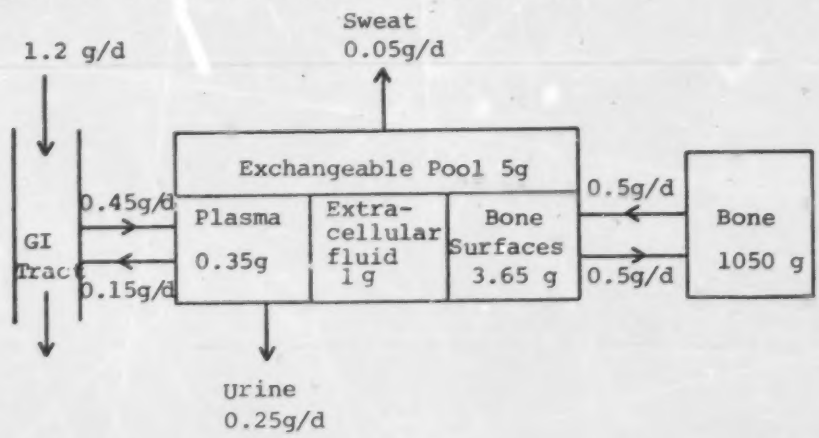


Figure C3: Model for Calcium Distribution.[18]



$\lambda + K$ is the effective elimination rate comprising both physical and biological factors. Thus effective half-life is defined as:

$$T_E = \frac{0.693}{\lambda + K} \qquad \text{(C 4)}$$

$$\text{or,} \quad \frac{1}{T_E} = \frac{1}{T_P} + \frac{1}{T_B} \qquad \text{(C 5)}$$

Where T_P is the physical half-life and T_B is the biological half-life, defined as

$$T_B = 0.693/K \qquad \text{(C 6)}$$

A second situation is one in which two compartments take part and where atoms transfer between the compartments in both directions. (Figure C 1b) If Q_1 is the activity in compartment one and Q_2 is the activity in compartment two, and if K_{12} is the transfer rate from compartment one to compartment two and K_{21} is the rate from two to one, with Q_0 the initial activity, then:

$$\frac{dQ_1}{dt} = -K_{12}Q_1 + K_{21}Q_2 \qquad \text{(C 7)}$$

$$\frac{dQ_2}{dt} + K_{12}Q_1 - K_{21}Q_2 \qquad \text{(C 8)}$$

with solutions of the form:

$$Q_1 = \frac{K_{12}}{K_{12} + K_{21}} Q_0 \left\{ \exp\left[-(K_{12} + K_{21})t \right] + \frac{K_{21}}{K_{12}} \right\} \qquad \text{(C 9)}$$

$$Q_2 = \frac{K_{12}}{K_{12} + K_{21}} Q_0 \left[1 - \exp - (K_{12} + K_{21})t \right] \qquad \text{(C 10)}$$

This form does not take into account physical decay.

The pathway for radium distribution is similar to that for

calcium. Radium is ingested, part is transferred to plasma, extracellular fluid and bone surfaces, which make up the exchangeable pool; part is excreted directly. (See Figure C 2) Of the part that goes to the pool, some radium is returned to the GI tract, some is transferred out as sweat and urine and some is transferred to the bone. Figure C 3 indicates the compartment model for calcium and gives quantities of Ca in each compartment. For radium, a much smaller amount is ingested, while that which is taken in is transferred almost exclusively to the bone from the exchangeable pool.

A second method of analysis is that of Marshall *et al*,[26] who start from a whole body retention function of the form:

$$R = (1-p)e^{-mt} + p\varepsilon^{b}\,(t-\varepsilon)^{-b}\left[\beta e^{-r\lambda t} + (1-\beta)e^{-\sigma r\lambda t}\right] \quad \text{(C 11)}$$

Where R = fraction of activity in bone after single injection.

ε = small time (0.3-3 days) related to the turnover of initial pool.

b = power function slope related to diffusion of activity from bone to blood, and excretion of part of activity.

λ = rate of apposition and resorption in compact bone.

σ = ratio of turnover of compact and cancellous bone.

β = fraction of bone volume activity deposited in compact bone.

γ = factor that corrects for deposition of activity in new bone sites.

m = rate constant of small early exponential in R.

p = fraction of R not in early exponential.

t = time.

The terms in the equation describe different long and short-term effects of radiation. The first term, $(1-p)e^{-mt}$, describes early effects, up to about a month after injection. If one used just a power function and ignored the exponential term, the results yielded would be lower than the data. Further, the introduction of this exponential term leads to higher turnover rates (λ) which agree

more closely with data on the formation rate of compact bone. In the second term the brackets indicate the deposition of activity in cancellous and compact bone (β is the fraction in compact bone), while the exponential factor and ε are introduced to produce good fits at times short and long after injection. Without ε, R becomes infinite when t goes to zero - a clearly non-physical result, while without the exponential, R increases without limit as t increases. One can then use this function to derive retention functions for local systems. The subdivisions used are: a) radioactivity in the body is divided into that in blood, soft tissue, and bone; b) radiation in bone is divided into that on bone surface and in bone volume; c) bone volume activity is divided into compact and cancellous bone activity; d) half of the surface activity is in compact and half in cancellous bone. The model can then be compared to available data.

Figure C 4 shows data from patients at Elgin State Hospital who were given radium injections in the 1930's. Along with this model prediction are those of several other models. The new model takes in account the variation in age and number of injections. Data on radium in the blood and skeleton are given in Figures C 5, C 6 and C 7. Data on prisoners in Stateville (Figure C 8) indicate the effect of continuous uptake. All of the data indicate fairly good agreement with the model. Tables C I and C II give the values of the parameters in the retention function for radium and the values of the function itself. A plot of these values is given in Figure C 9. As indicated there, the plasma initially contains a high level of activity which is transferred primarily to the bone. Surface levels of activity rise and fall rapidly while activity increases in bone volume up to 1000 days. A modification in the retention function for radium occurs because of differences in diminution between old and new compact bone.

Figure C4: Radium in Man - Whole Body Retention[26]

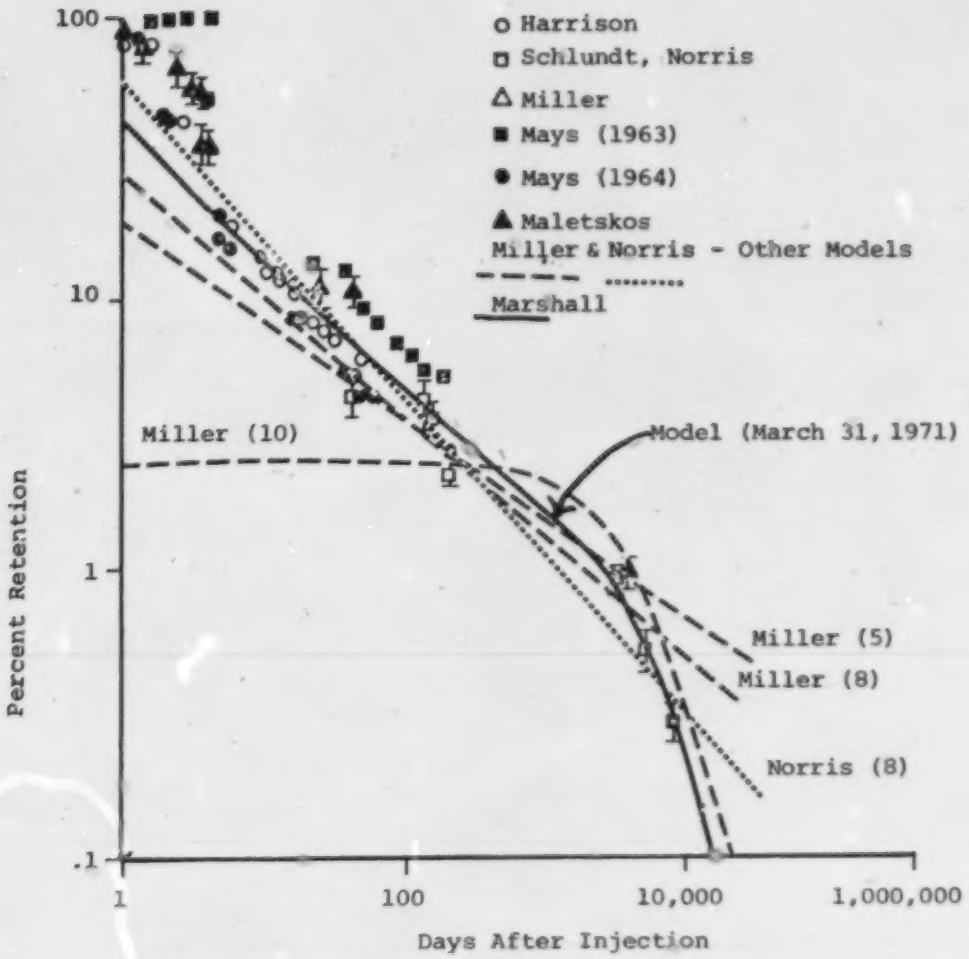


Figure C5: Plasma Radium in Man[26]

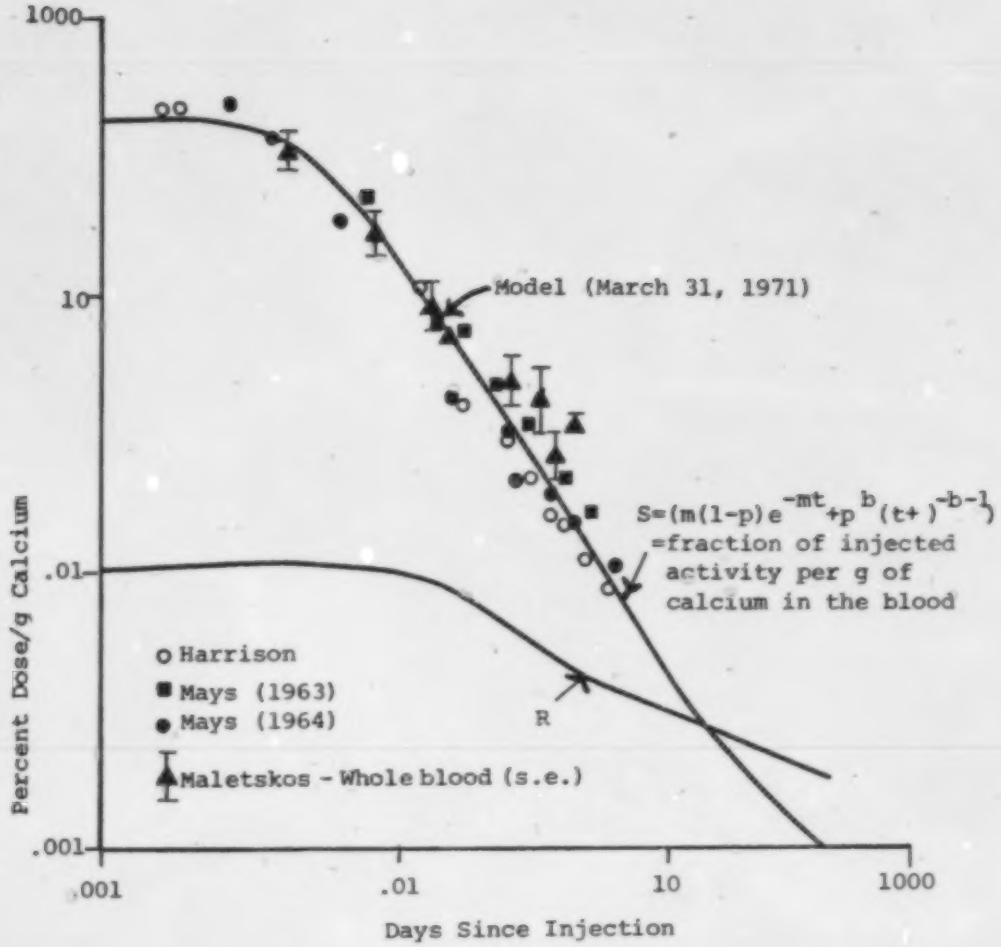


Figure C6: Radium in Man - Long-term Blood Measurements[26]

Ordinate shows the ratio

$$\frac{B - \text{Body activity per gram calcium } (B/S)_\infty}{S \quad \text{Serum activity per gram calcium}}$$

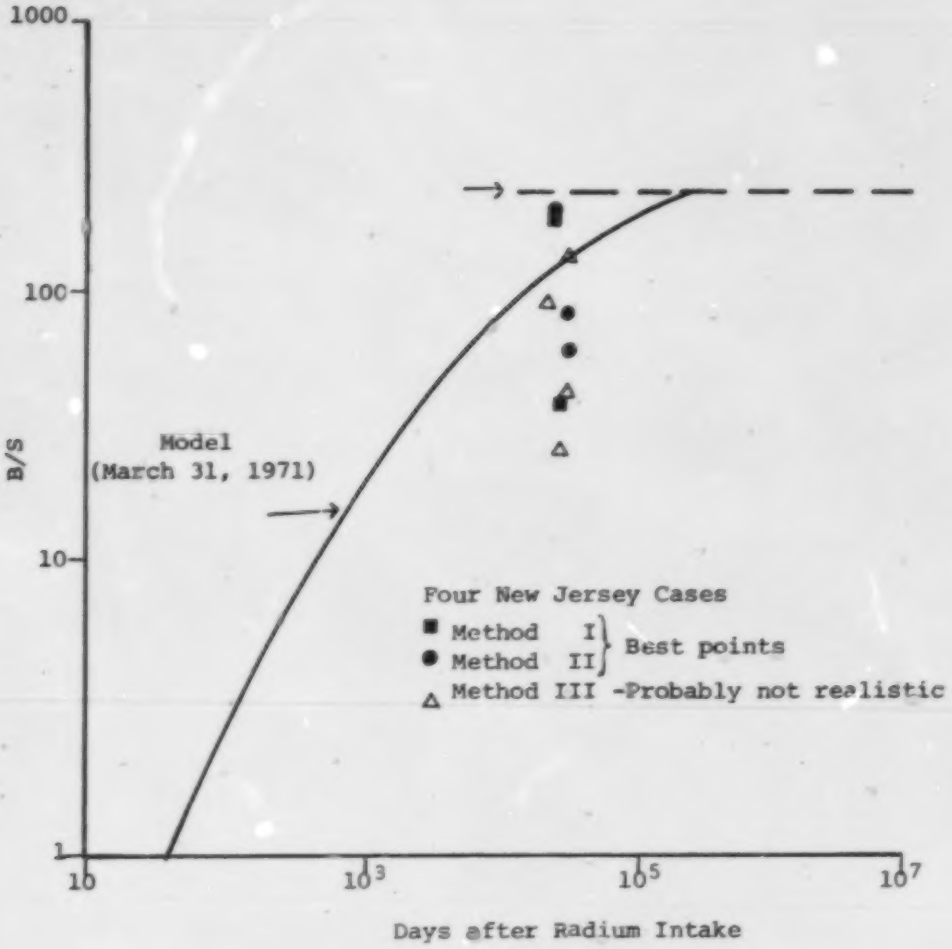


Figure C7: Radium in Man - Thoracic Vertebrae/ Skeleton[26]

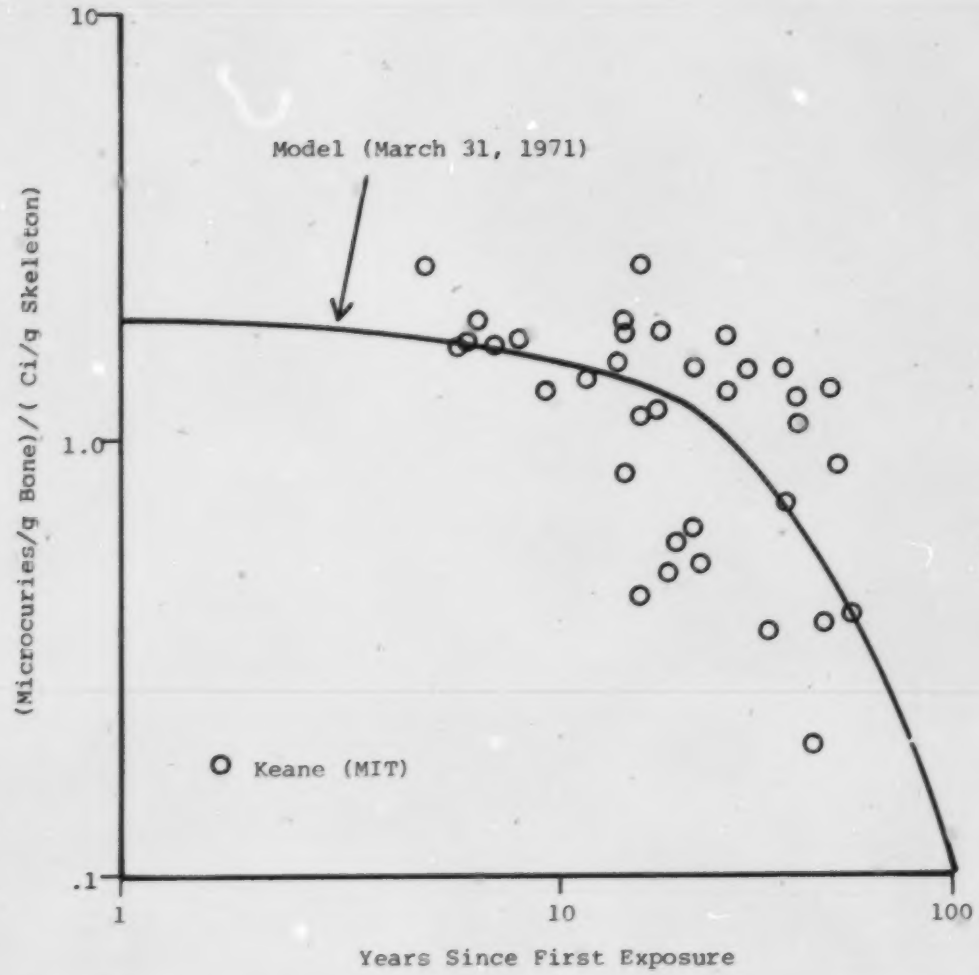


Figure C8: Radium in Man *versus* Time - Continuous Intake[26]

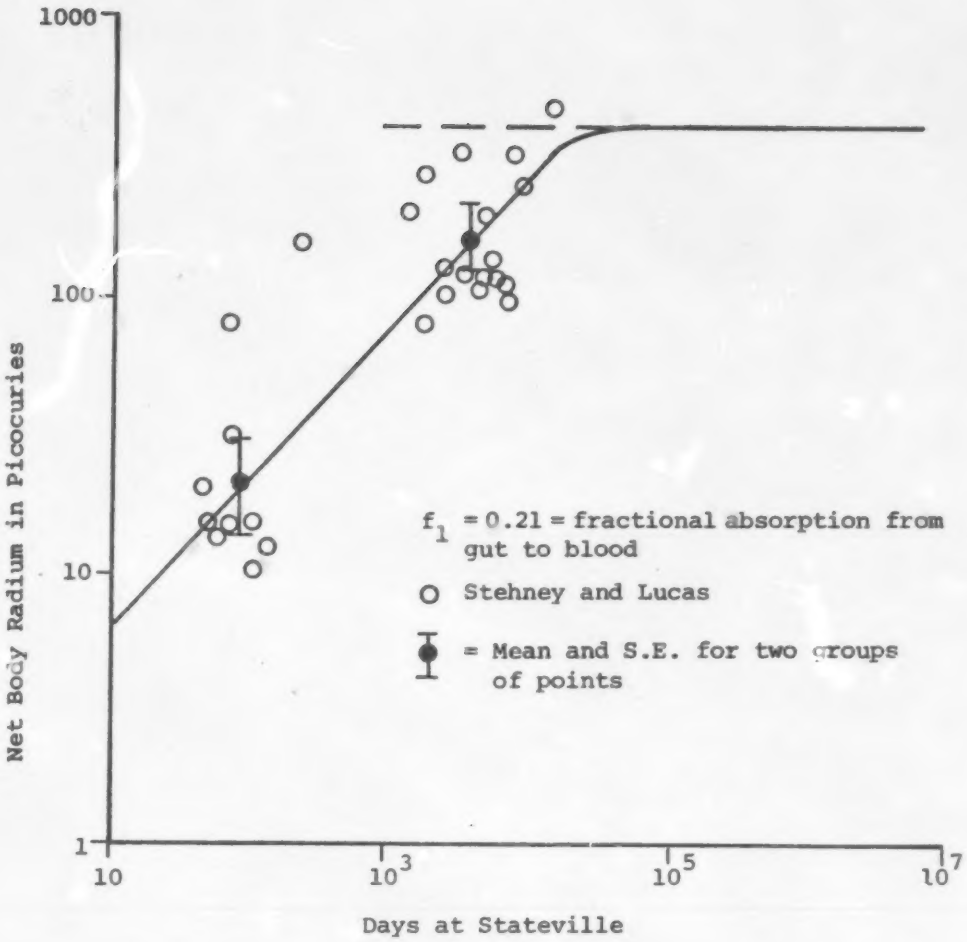


Figure C9: Radium in Man - Summary[26]

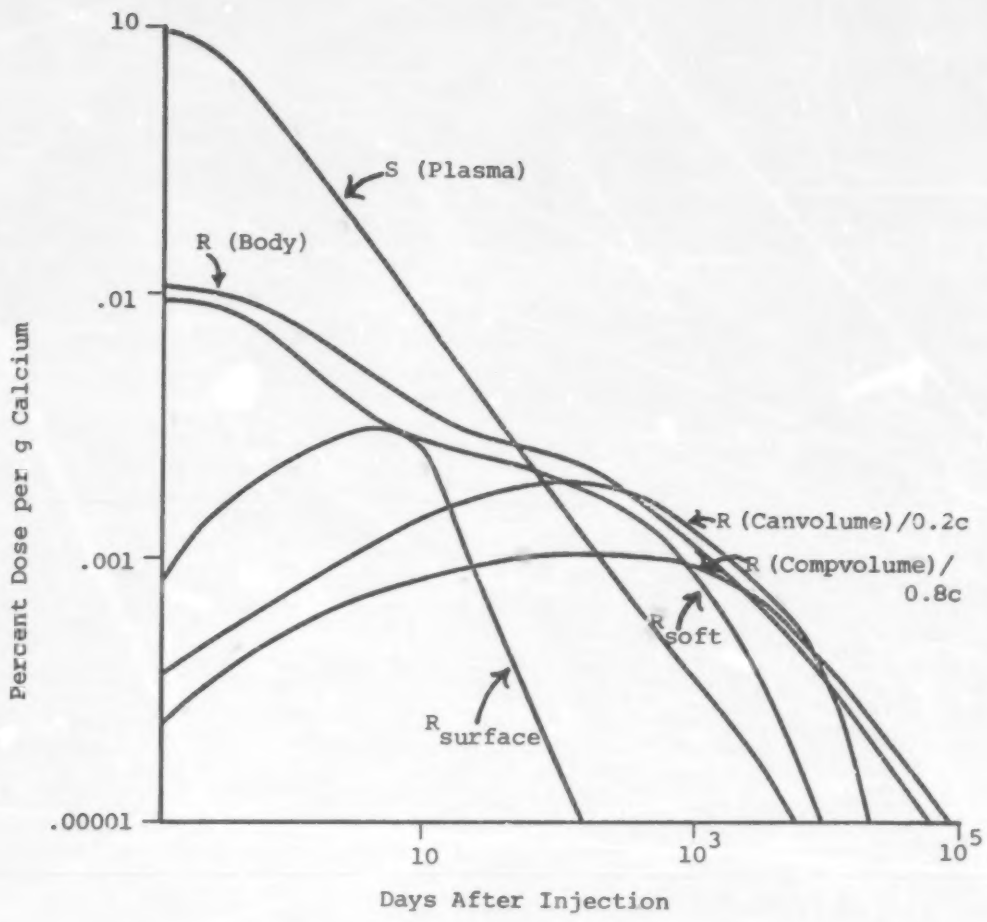


TABLE C I - Values of Parameters for Radium Retention Function[26]

Parameters	Units	Radium Model 3/31/71
Independent		
b	Dimensionless	0.415
	Day	0.12
	Percent/year	1.5
k	gm Ca/day	0.275
	Dimensionless	36.5
	Dimensionless	4
p	Dimensionless	0.821
m	Day^{-1}	0.4
	Dimensionless	1.31
c	gm Ca	1,000
c (surface)	gm Ca	12
	Day^{-1}	0.3
f_c	Dimensionless	3.0
f_l	Dimensionless	0.15-0.21
v_l	gm Ca/day	1
Dependent		
10 k	Liters/day	100
	Dimensionless	0.608
	Dimensionless	0.997
	Percent/year	52.0
	Percent	14.4
	Dimensionless	1.50
f_t	Dimensionless	1.94
Dif ratio	Dimensionless	1.87
t_x	Days	42
t_z	Years	21
(B/S)	Dimensionless	244

Table C II Percent of Injected Dose Versus Time After a Single Injection (Cf. Figure 18)[26]

Time (days)	Blood	Bone Surfaces	Soft Tissue	BONE VOLUME						Whole Body
				Compact		Cancellous		Compact	Cancellous Bone	
				New	Old	New	Old			
0.01	7.80	0.072	89.3	0.0119	0.0237	0.0119	0.0111	0.0716	0.0590	97.2
0.0316	6.30	1.94	83.8	0.0337	0.0670	0.0337	0.0316	1.07	1.04	92.2
0.1	3.81	5.94	70.9	0.0820	0.163	0.0820	0.0770	3.22	3.13	81.0
0.316	1.56	11.6	49.9	0.156	0.312	0.156	0.146	6.27	6.10	63.8
1.0	0.504	15.5	27.3	0.239	0.478	0.239	0.224	8.47	8.21	44.5
3.16	0.139	12.3	11.8	0.320	0.638	0.320	0.299	7.11	6.77	25.8
10.0	0.0198	2.48	9.01	0.374	0.742	0.373	0.346	2.36	1.96	13.3
31.6	0.00318	0.134	6.02	0.398	0.773	0.395	0.359	1.24	0.821	8.08
100.	0.000633	0.0253	3.04	0.415	0.757	0.403	0.344	1.18	0.760	4.99
316.	0.000127	0.00509	1.27	0.428	0.658	0.393	0.282	1.09	0.677	3.04
1,000.	0.0000266	0.00106	0.393	0.431	0.447	0.338	0.163	0.880	0.503	1.77
3,160.	0.0000058	0.000231	0.0830	0.381	0.203	0.205	0.0502	0.582	0.255	0.92
10,000.	0.0000011	0.000044	0.0112	0.233	0.0575	0.0493	0.00539	0.291	0.0547	0.35
31,600	0.0000001	0.000005	0.00079	0.0670	0.00870	0.000940	0.0000511	0.0757	0.00099	0.07

Appendix D - Glossary

Activity	The number of disintegrations in a given quantity of material per unit time.
Body Burden	The total quantity of radionuclide present in the body; Maximum Permissible Body Burden - The body burden of a radionuclide which, if maintained at a constant level, would produce the maximum permissible dose equivalent in the critical organ.
Cancellous Bone	Bone tissue that has a reticular or lattice-work structure.
Carcinoma	An epithelial cell new growth or malignant tumor, enclosed in connective tissue, and tending to infiltrate or give rise to metastases.
Cartilage	A type of dense connective tissue consisting of cells embedded in a ground substance or matrix.
Catalase	An enzyme present in cells which catalyzes the decomposition of hydrogen peroxide to water and oxygen.
Compact Bone	Hard or dense bone which forms the superficial layer of all bones.
Cortical Bone	The outer layer of the bone.
Curie	The unit of activity; it equals 3.7×10^{10} disintegrations per second.
Daughter	A stable or radioactive nuclide formed by radioactive decay.
Diaphysis	The shaft or middle part of a long cylindrical bone.
Dose	A term denoting the quantity of radiation or energy absorbed in a specified mass; Absorbed Dose - The energy imparted to matter in a volume element by ionizing radiation, divided by the mass of the irradiated material in that volume; Dose Equivalent - The product of absorbed dose, a quality factor, and other factors necessary to express on a common scale for all ionizing radiation the irradiation incurred by exposed persons; Maximum Permissible Dose Equivalent - (MPD), the largest dose equivalent received in a specified period which is permitted by a regulatory agency on the assumption that receipt of such a dose equivalent creates no appreciable somatic or genetic injury.
Endosteum	The membrane lining of the bone in the medullary cavity.

Genetically Significant Dose (GSD)	The dose which, if received by every member of the population, would be expected to produce the same total genetic injury to the population as do the actual doses received by various individuals.
Half-Life, Radioactive	For a single radioactive decay process, the time for the activity to decrease to half its value by that process: Half-Life, Biological - the time for the activity to decrease to half its value by biological process; Half-Life, Effective - the time for the activity to decrease to half its value by combination of physical and biological processes.
Half-Value Layer	The thickness of a specified substance which, when introduced into the path of a beam of radiation, reduces the value of a specific radiation quantity by half.
Haversian Canal	Minute vascular canals found in bone tissue.
Isotope	Nuclides having the same atomic number but different mass numbers.
Linear Energy Transfer (LET)	The transfer of energy along the path of a particle.
Lipids	The group of fat and fatlike substances characterized by their insolubility in water.
Mean Lethal Dose	The dose required to inactivate all entities if they continue to be inactivated at the initial rate.
Metaphysis	Portion of a developing long bone between epiphysis and diaphysis; the growing portion of bone.
Metastasis	Change in location of a disease or of its manifestation or transfer from one organ or part to another.
Nuclide	A species of atom characterized by its mass number, atomic number, and energy state of the nucleus, provided the mean life is long enough to be observable.
Osteoblast	A cell of mesodermal origin which is concerned with formation of bone.
Osteoclast	Giant multinuclear cell found in depressions on the surface of bone causing the entire resorption of the bone substance.
Osteogenesis	Formation and development of bone taking place in connective tissue or cartilage, ossification.
Periosteum	The fibrous membrane which forms the investing covering of bones except at their articular surfaces.
Quality Factor	A LET factor by which absorbed doses are to be multiplied to obtain the dose equivalent.

Rad	Unit of absorbed dose, one rad = 100 ergs / gram.
Relative Biological Effectiveness (RBE)	The inverse ratio of the dose in rads of two radiations required to produce the same biological effects.
Rem	Roentgen equivalent in man, the unit of dose equivalent.
Roentgen	The unit of exposure, the quantity of X or Y radiation such that the associated corpuscular emission per 0.001293 gram air produces in air ions carrying one esu of electricity.
Sarcoma	Cancer arising from underlying tissue.
Trabecular Bone	Fibrous cord of connective tissue serving as a supporting fiber.

REFERENCES

1. "Report of Committee II on Permissible Dose for Internal Radiation." ICRP Publication 2, 1959, Pergamon Press, New York, N.Y. (Cited in reference 7)

2. "Report of the Task Group on Reference Man," ICRP Publication 23, 1975. Pergamon Press, New York, N.Y. (Cited in reference 7).

3. "The Effects on Population of Exposure to Low Levels of Ionizing Radiation." Report of the Advisory Committee on the Biological Effects on Ionizing Radiation. Division of Medical Sciences, National Academy of Sciences, National Research Council. Washington, D.C., November, 1972. (Cited in reference 7).

4. "Background Material for the Development of Radiation Protection Standards," Federal Radiation Council, Report #2, U.S. Department H.E.W., USPHS, Washington, D.C., September, 1961. (Cited in reference 7).

5. Gofman, John W. and Tamplin, Arthur R.: "Epidemiological Studies of Carcinogenesis by Ionizing Radiation," Proceedings of the Sixth Berkeley Symposium on Mathematical Statistics and Probability, held at the Statistical Laboratory, University of California, University of California Press, 1970.

6. Evans, R. D.: "The Radium Standard for Boneseekers - Evaluation of the Data on Radium Patients and Dial Painters," Health Physics 13, 267, 1967.

7. U.S. Environmental Protection Agency: "Statement of Basis and Purpose for the Proposed National Interim Primary Drinking Water Regulations: Radioactivity." August 15, 1975.

8. Jones, H. B. and Grendon, A.: "Environmental Factors in the Origin of Cancer and Estimation of the Possible Hazard to Man," Fd. Cosmet. Toxicol. 13, 251, 1975.

9. Peterson, Norman J., Samuels, Larry D., Lucas, Henry F. and Abrahams, Simon P.: "An Epidemiologic Approach to Low-Level Radium-226 Exposure," Public Health Report, 81, 805, 1966.

10. Taylor, D. M., Bligh, P. H. and Duggan, M. H.: "The Absorption of Calcium, Strontium, Barium and Radium from the Gastro-intestinal Tract of the Rat." Biochem. J., 83, 25, 1962.

11. Lucas, Henry F.: "Improved Low-Level Alpha - Scintillation Counter for Radon, The Review of Scientific Instruments, 28, 680, 1957.

12. Personal Communication of Christine Riddiough and Rod Musselman to Henry F. Lucas, November 20, 1975.

13. Lucas, Henry F. Jr. and Ilcewicz, F. H.: "Natural Radium - 226 Content of Illinois Water Supplies," J. of American Water Works Association, 50, 1523, 1958.

14. Hursh, J. P.: Radium Content of Public Water Supplies," J. of American Water Works Association, 46, 5, 1954.

15. Samuels, L. D.: "A Study of Environmental Exposure to Radium in Drinking Water," in Natural Radiation Environment, Ed. by J. A. Adams and W. M. Lowder, University of Chicago Press, Chicago, 1964, pp. 239-251.

16. Bureau of the Census: General Population Characteristics: Illinois, U.S. Department of Commerce, PC (1) - B15, Illinois, October, 1971.

17. Brooks, A. L.: "Chromosome Damage in Liver Cells from Low Dose Rate Alpha, Beta and Gamma Irradiation: Derivation of RBE," Science, 190, 1975.

18. Johns, H. E. and Cunningham, J. R.: "The Physics of Radiology," Charles C. Thomas, Springfield, Illinois, 1969.

19. Spiers, F. W.: Radioisotopes in the Human Body: Physical and Biological Aspects. New York and London, Academic Press, 1968.

20. Marshall, J. H.: "The Retention of Radionuclides," from The Delayed Effects of Bone Seeking Radionuclides, Ed. by C. W. Mays, *et al*. Salt Lake City, Utah, University of Utah Press, 1969.

21. Samuels, L. D.: "Uptake of Radium - 226 From Drinking Water into Human Deciduous Teeth,: Arch. Oral Biology, 11, 581, 1966.

22. Walton, A., Kologrivov, R., and Kolp, J. L.: "The Concentration and Distribution of Radium in the Normal Human Skeleton," Health Physics, 1, 409, 1959.

23. Spencer, H., Kramer, L. and Samachson, J.: "Intake and Excretion Patterns in Naturally Occurring Radium - 226 in Humans," Radiation Research, 56, 354, 1973.

24. Muller, J., Klener, V., Tuscany, R., Thomas, J., Brezikova, D. and Houskova, M.: "Study of the Internal Contamination with Strontium - 90 and Radium - 226 in Man in Relation to Clinical Findings," Health Physics, 12, 993, 1966.

25. Tsai, H. C. C., Della Rosa, R. J., Rosenblatt, L. S., and Nix, N.: "Radium - 226 Effects on the Mucopolysaccharides of Cartilage," Health Physics, 18, 17, 1970.

26. Marshall, J. H., Lloyd, E. L., Rundo, J., Liniecki, J., Marotti, G., Mays, C. W., Sisson, H. A., and Snyder, W. W.: Alkaline Earth Metabolism in Adult Man, London, Pergamon Press, 1972.

27. Annual Report of the University of Utah, "Work in Progress in the Internal Irradiation Program," COO - 119 - 240 (1969). Cited in Chiacchierini, R. P. *et al*: "A Review of Radium Toxicity Studies," Division of Biological Effects. U.S. Dept. HEW, Public Health Service, December, 1970.

28. Dougherty, T. F. and Mays, C. W.: "Bone Cancer Induced by Internally-Deposited Emitters in Beagles," in Radiation-Induced Cancer, Ed. by A. Ericson. International Atomic Energy Agency, Vienna, 1969. cited in Chiacchierini, R. P., *et al*, "A Review of Radium Toxicity Studies," Division of Biological Effects, U.S. Dept. HEW, Public Health Service, December, 1970.

29. "Annual Report of the University of California, Davis, Radiobiology Laboratory, UCD 472 - 116 (1969) cited in Chiacchierini, R. P., *et al*, "A Review of Radium Toxicity Studies," Division of Biological Effects, U.S. Dept. HEW, Public Health Service, December, 1970.

30. Finkel, M. P., Bisko, B. O., and Jenkins, P. B.: "Toxicity of Radium - 226 in Mice," in Radiation Induced Cancer Ed. by A. Ericson, International Atomic Energy Agency, Vienna, 1969. cited in Chiacchierini, R. P., *et al*: "A Review of Radium Toxicity Studies," Division of Biological Effects, U.S. Dept. HEW Public Health Service, December, 1970.

31. Goldman, M., Dungworth, D. L., Bulgin, M. S., Rosenblatt, L. S., Richards, W. P. C. and Burtad, L. K.: "Radiation-Induced Neoplasms in Beagles after Administration of ^{90}Sr and ^{226}Ra." in Radiation Induced Cancer, Ed. by A. Ericson, International Atomic Energy Agency, Vienna, 1969.

32. Momeni, M. H., William, R. J. R., Fisher, G. L. and Rosenblatt, L. S.: "Local Dosimetry and Qualitative Changes in ^{226}Ra and ^{90}Sr Labeled Beagle Humeri," Health Physics, 30, 21, 1976.

33. Miller, C. E., Hasterlik, R. J. and Finkel, A. J.: The Argonne Radium Studies - Summary of Fundamental Data," ANL-753 and ACFH-106, Argonne National Laboratory and Argonne Cancer Research Hospital, January, 1969.

34. Finkel, A. J., Miller, C. E. and Hasterlik, R. J.: "Radium-Induced Malignant Tumors in Man," in Delayed Effects of Bone-Seeking Radionuclides, Ed. by C. W. Mays, *et al*, pp 195-225. University of Utah Press, Salt Lake City, Utah, 1969.

35. Goss, S. G.: "The Malignant Tumor Risk from Radium Body Burden," Health Physics, 19, 731, 1970.

36. Sharpe, William D.: "Chronic Radium Intoxication: Clinical and Autopsy Findings in Long-Term New Jersey Survivors," Environmental Research, 8, 243, 1974.

37. Rowland, R. E., Failla, P. M., Keane, A. T. and Stehney, A. F.: "Some Dose-Response Relationships for Tumor Incidence in Radiation Patients," Argonne National Laboratory, Radiological Physics Division Annual Report, Center for Human Radiobiology, ANL - 7760, Part II, pp. 1-17, July, 1969 - June, 1970.

38. Spiess, H. and Mays, C. W.: "Protraction Effect on Bone Sarcoma Induction of ^{224}Radium in Children and Adults," presented at the Radionuclide Carcinogenesis Symposium, Richland, Washington, May 11-13, 1972.

39. da Horta, S. J. and da Motta, L. C.: "Follow-up Study of Thorium Dioxide Patients in Portugal," Annals of New York Academy of Sciences, 145, 830, 1967.

40. Dudley, Robert A.: "A Survey of Radiation Dosimetry in Thorium Dioxide Cases," Annals of New York Academy of Sciences, 145, 859, 1967.

41. Faber, M.: "Thorium Dioxide Patients in Denmark," Annals New York Academy of Sciences, 145, 843, 1967.

42. Lundin, F. E., Jr., Wagoner, J. K. and Archer, V. E.: "Radon Daughter Exposure and Respiratory Cancer: Quantitative and Temporal Aspects," National Institute for Occupational Safety and Health, National Institute of Environmental Health Sciences, Joint Monograph No. 1, June, 1971.

43. Wagoner, J. K., Archer, V. E., Holaday, D. D. and Lloyd, J. W.: "Radiation as the Cause of Lung Cancer Among Uranium Workers," New England Journal of Medicine, 273, 181, 1965.

44. U.S. Environmental Protection Agency: "Interim Primary Drinking Water Regulation: Proposed Maximum Contaminant Levels for Radioactivity," Federal Register, August 14, 1975, pp. 34324-34328.

45. "Report of the RBE Committee to the International Commission on Radiological Protection and on Radiological Units and Measurements," Health Physics, 9, 357, 1963.

46. Casarett, Allison P.: Radiation Biology, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1968.

47. National Council on Radiation Protection and Measurements: "Basic Radiation Protection Criteria," NCRP Report No. 39, Washington, D.C., January 15, 1975.

48. National Council on Radiation Protection and Measurements: "Review of the Current State of Radiation Protection Philosophy," NCRP Report No. 43, Washington, D.C., January 15, 1975.

49. Evans, R. D., Keane, A. T., Kolenkow, R. J., Neal, W. R., and Shanahan, M. M.: "Radiogenic Tumors in the Radium and Mesothorium Cases Studied at M.I.T.," pp. 157-194, in Delayed Effects of Bone-Seeking Radionuclides, Ed. by C. W. Mays, *et al*, University of Utah Press, Salt Lake City, Utah, 1969.

50. Massachusetts Institute of Technology, Radioactivity Center, Department of Physics, Annual Progress Report, MIT - 952 - 6 (1969).

51. Evans, R. D.: "The Effect of Skeletally Deposited Alpha-Ray Emitters in Man," British J. of Radiology, 39:881-895 (1966).

52. Lucas, Henry F., Jr.: "Correlation of the Natural Radioactivity of the Human Body to That of Its Environment" Uptake and Retention of Radium 226 from Food and Water, U.S. Atomic Energy Commission, Argonne National Laboratory, ANL - 6297, February, 1961.

53. Stehney, A. F. and Lucas, H. F., Jr.: "Studies on Radium Content of Humans Arising from Natural Radium of their Environment," Proceedings of International Conference on Peaceful Uses for Atomic Energy, held in Geneva, August, 1955. New York, United Nations, 11, 49-54, 1956. (Cited in reference 1)

54. Schjeide, O. A. and Develus, J.: "Mechanisms of Radiation Damage in the Mammalian Fetus and Neonate," in, Radiation Biology of the Fetal and Juvenile Mammal, Ed. by M. R. Sikov and D. D. Mahlum. U. S. Atomic Energy Commission, Washington, D.C., 1969.

55. Arena, V.: Ionizing Radiation and Life. C. V. Mosby and Co., St. Louis, Missouri, 1971.

56. Einck-Rosskamp, P., Rajewsky, B. and Strahlhofen, W.: "Cross-Placental Passage of Radium-228 and its Daughters After Intravenous Injection of Colloidal Thorium Dioxide (Thorotrast) into Rabbits." in Radiation Biology of the Fetal and Juvenile Mammal, Ed. by M. R. Sikov and D. D. Mahlum. U.S. Atomic Energy Commission, Washington, D.C., 1969.

57. Taylor, C. V., Thomas, F. O. and Brown, M. G.: "Studies on Protozoa," in Lethal Effects of the X-Radiation of a Sterile Culture Medium for *Colpidum Campylum.*" Physiol. Zool. 6, 467, 1933.

58. Aebi, H., Heiniger, J. P. and Lauber, E.: "Methamoglobinbildung in Erythrocyten Durch Peroxidein Wirkung. Versuche Fur Buerteilung Der Schutzfunktion Von Katalase Und Glutathion-peroxidase." Hel. Chim. Acta, 47, 1428, 1964.

59. Thomson, J. F.: "Possible Role of Catalase in Radiation Effects on Mammals." Rad. Res. Supp., 3, 93, 1963.

60. Latarjet, R., Ekert, B. and Demerseman, P.: "Peroxidation of Nucleic Acids by Radiation: Biological Implications." Rad. Res. Supp., 3, 247, 1963.

61. State of Illinois, Population at Risk, EHRC, in preparation.

62. Ezekiel, E.: "Intestinal Iron Absorption by Neonates and Some Factors Affecting It," J. Lab. Clin. Med., 70, 138, 1967.

63. Barron, E. S. G. and Dickman, S.: "Studies on the Mechanism of Ionizing Radiation: II. Inhibition of Sulfhydryl Enzymes by Alpha, Beta and Gamma Rays." J. Gen. Physiology, 32, 595, 1949.